Coursebook

Organic Chemistry

Reaction Mechanisms

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Content

I. Solvents

I. 1. Definition

By definition, a solvent is a chemical substance that can be solid, liquid, or gas in which reactants "solutes" dissolve resulting in a miscible mixture known as "solution". Furthermore, the amount of a solute that can be dissolved in a specific volume of a solvent is subjected to several factor including temperature, pressure, and stirring. As a result, we can distinguish four types of solutions:

- Diluted solutions that contain very low amount of solute.
- Concentrated solutions that contain the maximum amount of solute that can be dissolved at standard conditions.
- Saturated solutions contain more than the maximum amount of solute. In this case, the solution is exposed to high temperature in order to dissolve more molecules of the solute.
- Supersaturated solution, which contain more dissolved solute than required for a saturated solution. This type of solutions can be prepared by heating a saturated solution while adding more solute, then cooling it gently.

I. 2. Solvent Classification

In chemistry, solvents can be classified in several categories depending upon their chemical and physical properties. For instance, they are divided into two classes "polar solvents, and apolar solvents" based on their polarity.

I. 2. 1. Apolar Solvents

The vast majority of organic solvents are considered apolar solvents; they have either a frail dipole-dipole moments "polarizable inert solvents", or not at all "inert solvents". These solvents are mostly used when dissolving non-polar species.

I. 2. 2. Polar Solvents

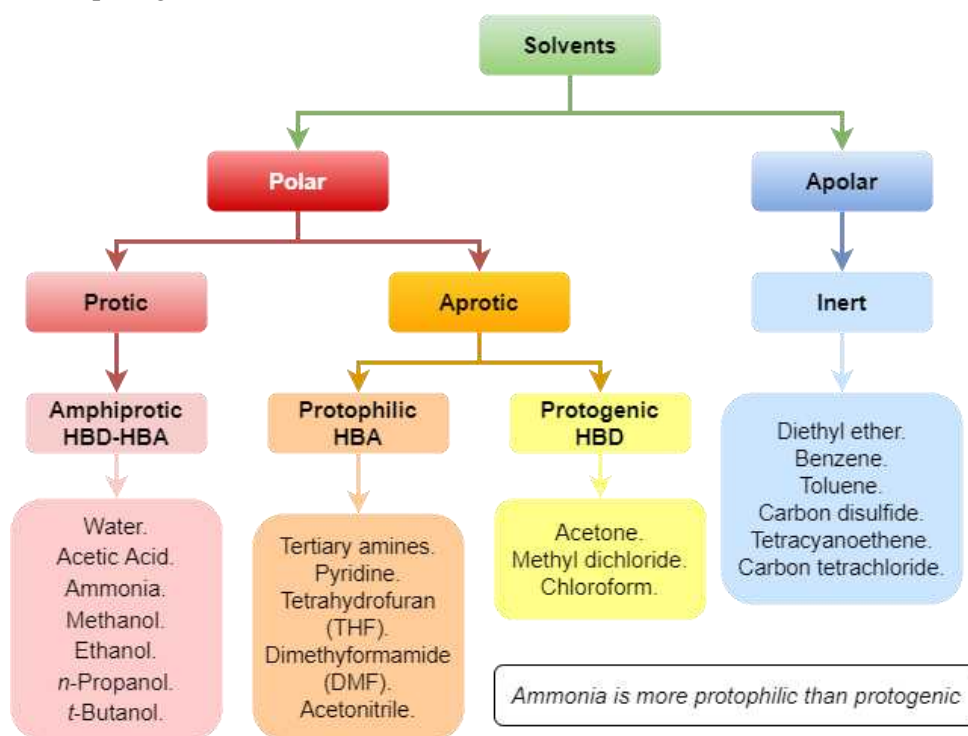
Polar solvents are chemical substances that exhibit dipole-dipole moments, in other word, they have a positive side, which represents the least electronegative atom(s), and a negative side where there is the most electronegative atom or group of atoms. Moreover, polar solvents are further subdivided into two sub-classes "protic, and aprotic" based on whether they can form intermolecular hydrogen bonds among themselves or not.

I. 2. 2. 1. Protic Solvents

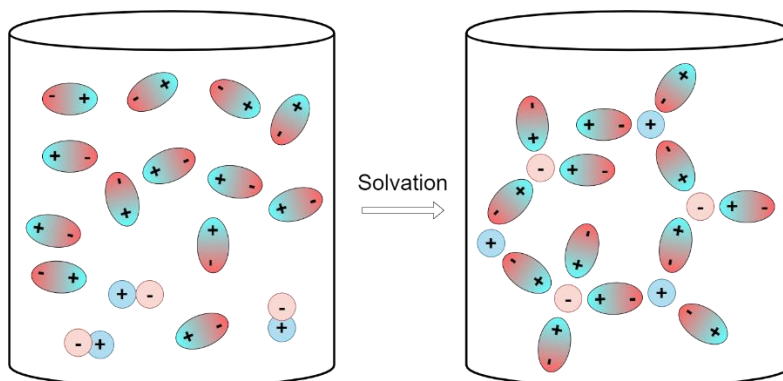
Protic solvents are characterized by their ability to form intermolecular hydrogen bonds among themselves. These solvents should therefore possess certain

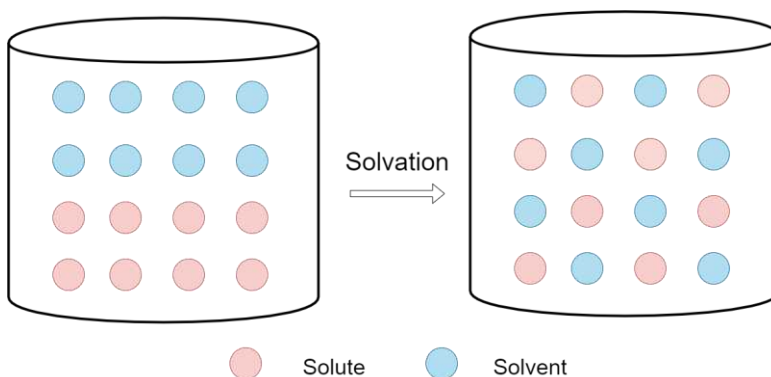
functional group such as –OH, –SH, or $-NH_2$. Protic solvents are also referred to as amphiprotic solvents due to their ability to donate or accept hydrogen prot on depending upon the medium in which they are. The term **amphoteric** is derived from the Greek word *ἀμφότεροι* [*amphoteroi*], which means "both" while protic refers to protons H^+.

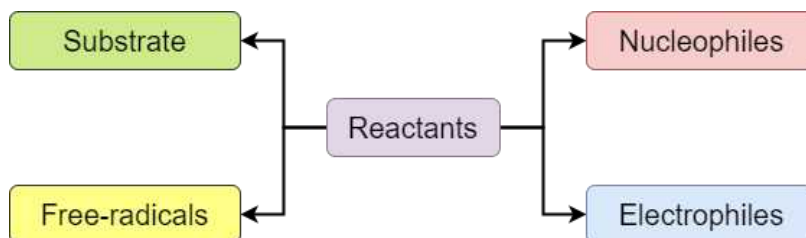
I. 2. 2. 2. Aprotic Solvents

Aprotic solvents, on the other hand, cannot fo rm intermolecular hydrogen bonds among themselves; however, they can be hydrogen -bonds acceptors HBA , also known as protophilic solvents, such as THF, and DMF, or hydrogen-bonds donors HBD "protogenic" such as acetone.

I. 3. Solubility

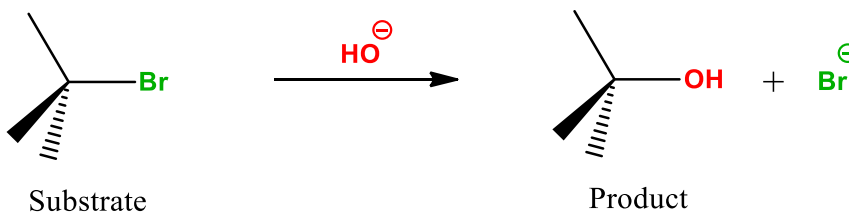
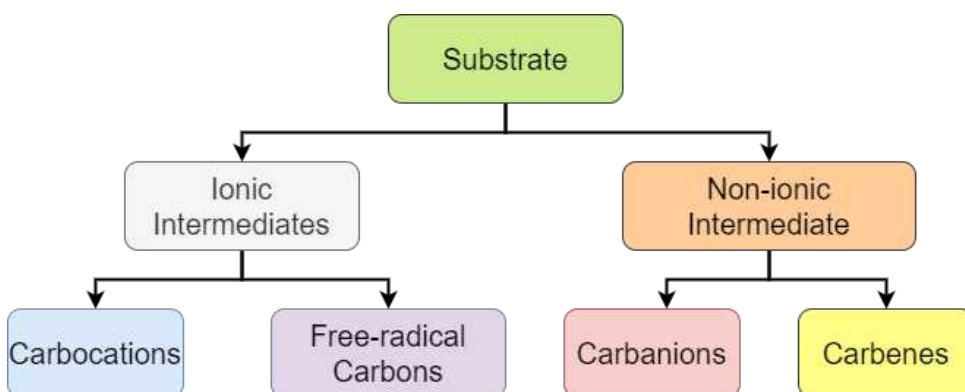
As the famous aphorism says "likes dissolve likes", substances tend to dissolve in solvents that have similar polarity with them. As a result, polar solutes dissolve in polar solvents whereas apolar solutes dissolve in non -polar solvents. This phenomenon is called solvation and it can be explained through the intermolecular forces between solvent -solute molec ules and the change of entropy. For polar

compounds, dipole-dipole and ion-dipole forces and in case of protic solvent, hydrogen bonds facilitate the solvation of solute in the solvent.

Dissolution of polar solutes in polar solvents.

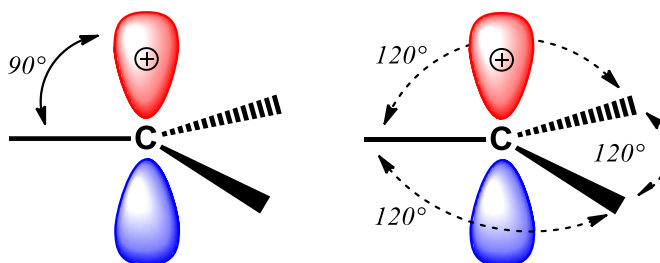
On the other hand, apolar compounds dissolve in apolar solvents due to the entropy change since these substances have only frail London forces, which are too weak to form a solution alone.

Dissolution of apolar solutes in apolar solvents.

Reactants are the starting materials of a c hemical reaction, which react with one another to form new chemical bonds as other bonds break. In organic reactions, reactants include substrates, free radicals, nucleophiles, and electrophiles.

II. 1. Substrate

In organic chemistry, a substrate is a molecule that reacts with other reactants to produce one or more products. These organic molecules can be anything that has a reactive site such as multiple bounds in alkenes, alkynes, and arenes, or a molecule that contains at least one leaving group such as alkyl halides.

➲ ***Example***

At the course of a chemical reaction, the substrate may or may not pass through the formation of short-living fragment called "intermediate", which can be ionic or non-ionic based on how bonds break. Homolytic cleavage results in the formation of non-ionic intermediates such as free-radical carbons and carbene. On the other hand, heterolytic cleavage gives ionic intermediates that include carbocations and carbanions.

II. 1. 1. Carbocation

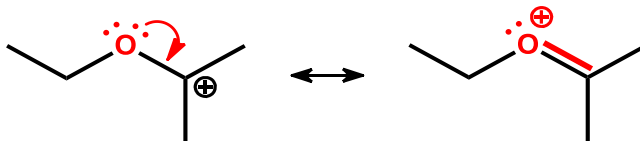
II. 1. 1. 1. Definition and Structure

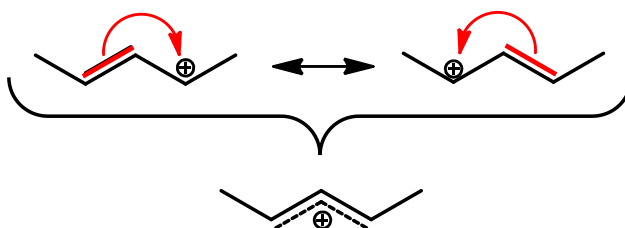
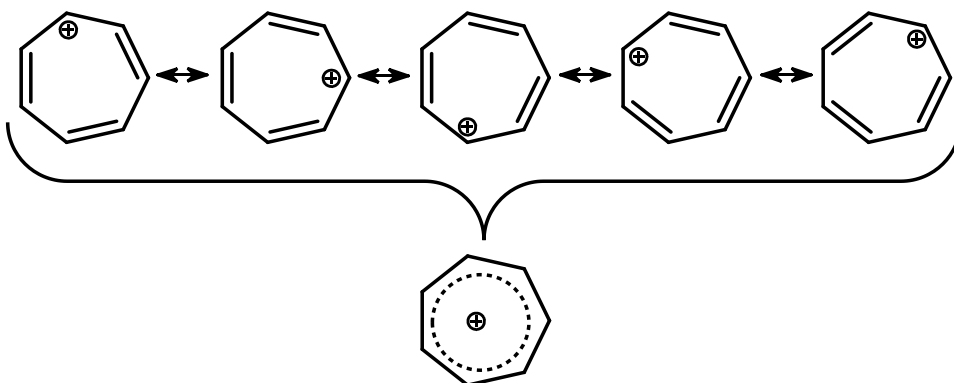
Carbocations are sp^2 hybridized carbon atoms that bear a positive charge (+1) with a vacant p orbital. These particular species have a planar geometry where the three substituents lay on the same plane, 120° away from one another with the vacant p orbital perpendicular on the plane.

II. 1. 1. 2. Stability

Since carbocations are electron deficient species, their stability increases when minimizing the positive charge. Consequently, the stability of carbocations varies according to the factors listed below.

Resonance

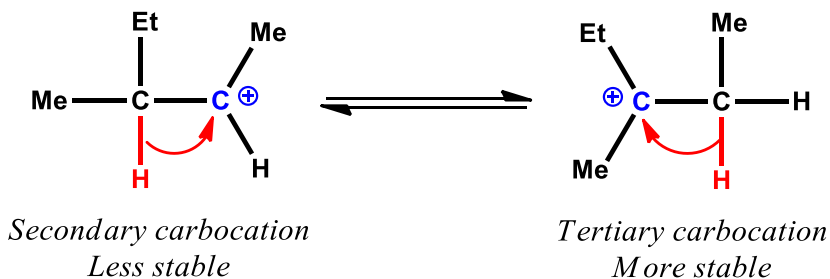
Electron-releasing groups ERG s help in del ocalizing the positive charge of the carbocation through the positive mesomeric effect+*M* and as a result, they improve

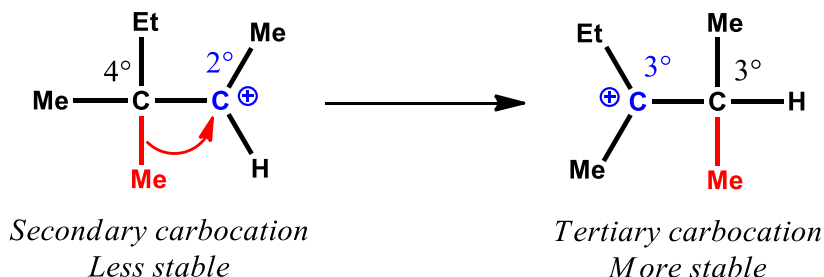
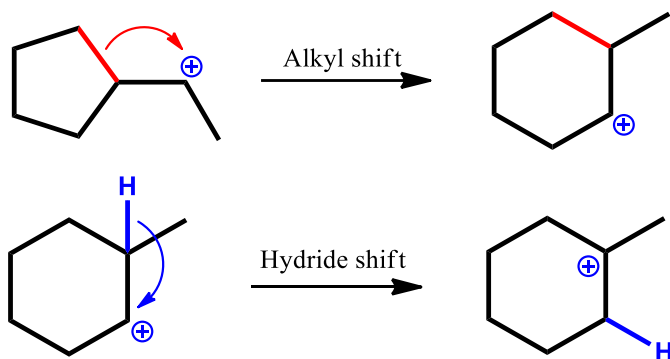
its stability. In contrast, electron-withdrawing groups EWGs that exhibit negative mesomeric effect -*M* destabilize carbocations.

Similarly, in case the carbocation belongs to an allylic or an aromatic system, resonance stabilizes the carbocation by delocalizing the positive charge on multiple positions.

In allylic systems

In aromatic systems

Hyperconjugation

Hyperconjugation, also known as σ-conjugation, describes the stabilizing interaction that results from the interaction of the electrons in a σ- bond, usually C–H or C–C, with an adjacent empty or partially filled p-orbital in order to form a more stabilized system. There are three types of hyperconjugations known in organic chemistry:

1, 2-Hydride Shift

In this case, a hydride ion would migrate to the adjacent carbocation, which leads to the delocalization of the positive charge into a more substituted carbon atom.

1,2-Alkyl Shift

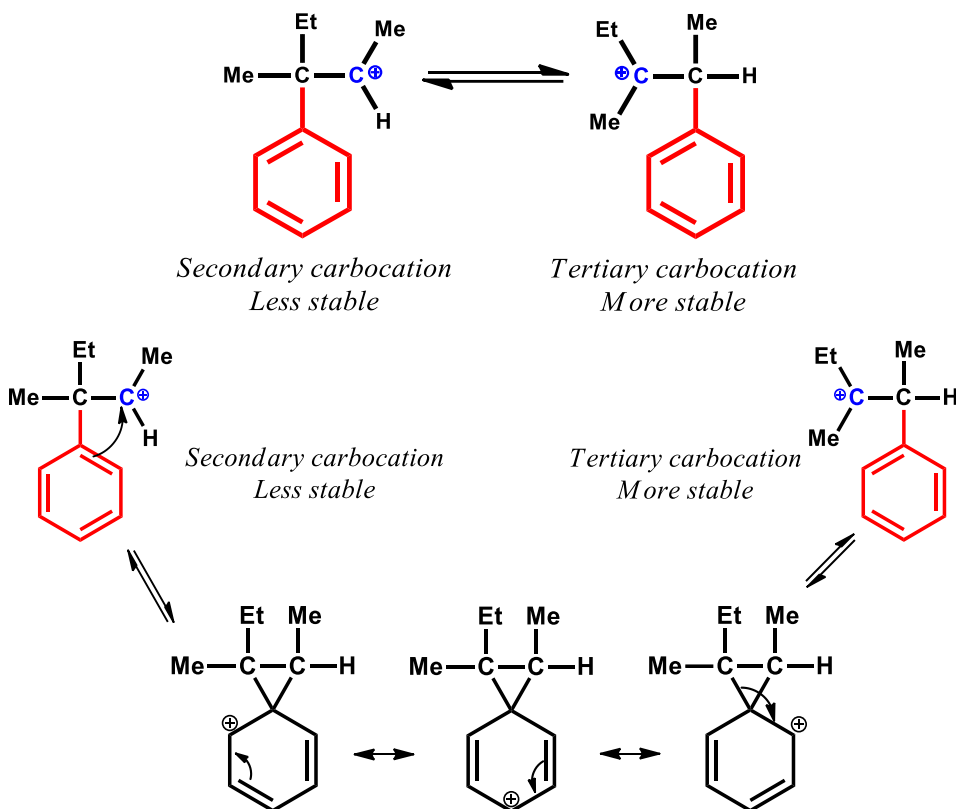
1,2-alkyl shift denotes carbocation rearrangement from a less stable state to a more stable one. For example, if a carbocation forms on a secondary carbon and there is an adjacent quaternary carbon, an alkyl shift will take place in order to form a tertiary carbocation on this adjacent carbon atom.

Carbocation rearrangement through alkyl shift is also common when the carbocation is adjacent to a cyclic ring.

1,2-Aryl Shift

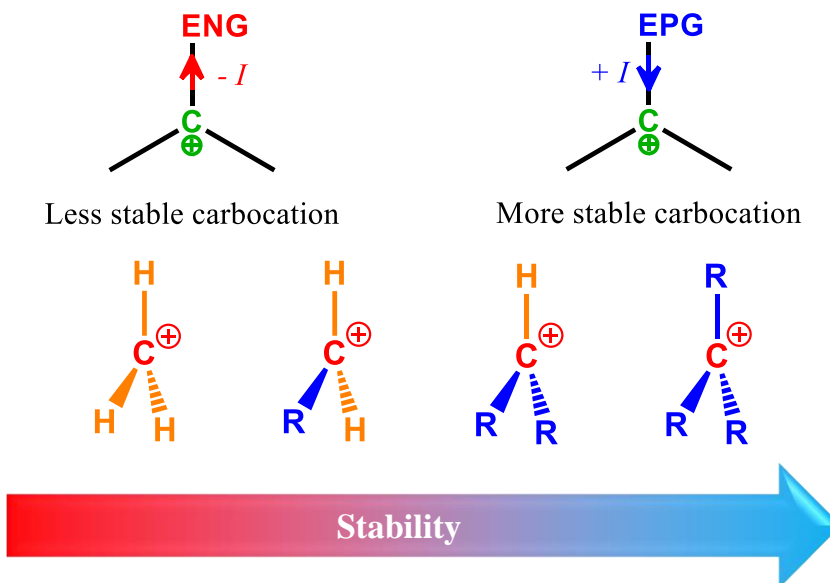
1,2-aryl shift is a carbocation rearrangement in which an aryl group migrates towards the adjacent carbon atom bearing the positive charge.

Secondary carbocation
Less stable

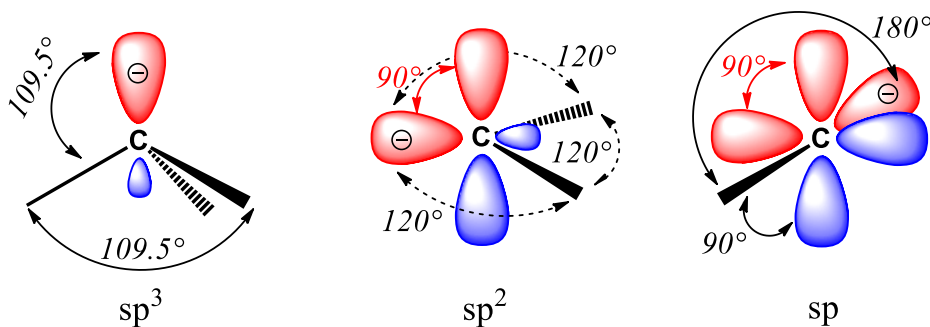
Tertiary carbocation
More stable

Secondary carbocation
Less stable

Tertiary carbocation
More stable

Inductive Effect

Positive inductive effect $+I$ induced by electropositive groups (EPG) enhances the stability of carbocations while negative inductive effect $-I$ caused by electronegative groups (ENG) destabilizes carbocations. As a result, tertiary carbocations are more stable whereas methylium ions a re the least stable carbocations.

II. 1. 2. Carbanion

II. 1. 2. 1. Definition and Structure

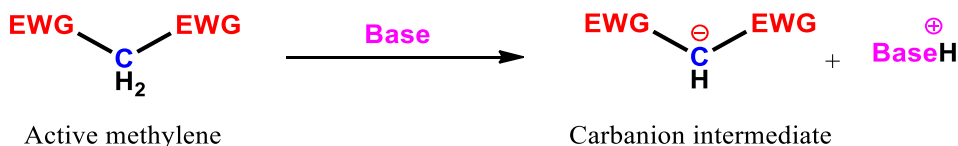
A carbanion is a carbon atom that has an unshared pair of electrons and bears a negative charge (-1). This particular anion can have a trigonal pyramidal geometry when it is tri-substituted carbanion **(sp^3)**, a bent geometry when it is bi-substituted **(sp^2)**, or a linear geometry in case of mono-substituted carbanions **(sp)**.

II. 1. 2. 2. Stability

Because carbanions are electron rich species, their stability depends upon minimizing the negative charge of the carbanion by resonance, hybridization, or inductive effect.

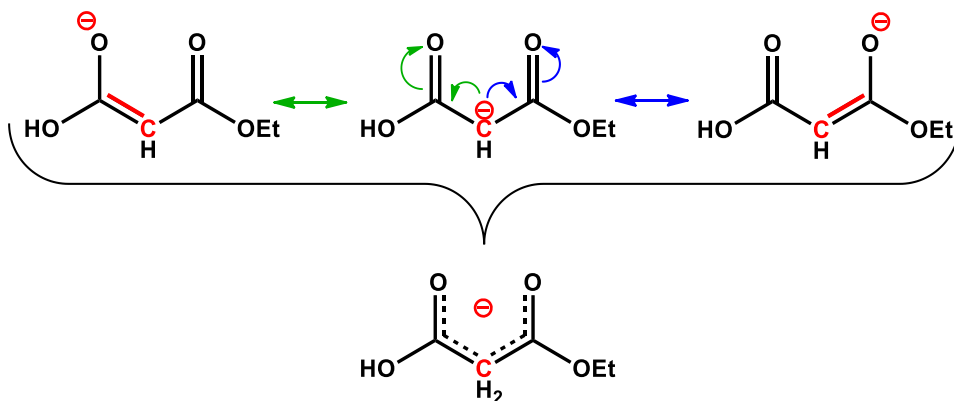
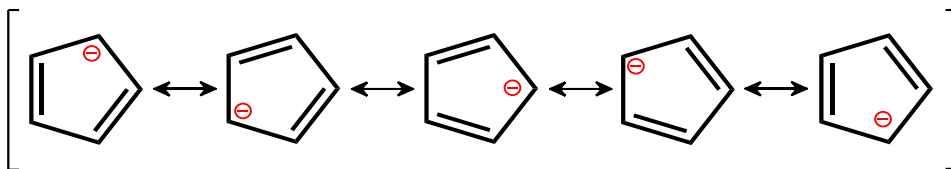
Resonance

Unlike carbocations, carbanions are stabilized with electron -withdrawing groups. Active methylene compounds are excellent example to demonstrate how EWGs increase the stability of carbanions.

Active methylene is a methyl group attached to two EWGs. These two EWGs pull valence electrons of the carbon atom they are attached to resulting in an acidic C-H bond. When an active methylene compound is treated with a base, one hydrogen atom would be abstracted leaving a full negative charge on the carbon atom it was attached to.

Active methylene Carbanion intermediate

Once the carbanion is formed, the negative mesomeric effect -*M* would stabilize it by delocalizing the negative charge on two other positions.

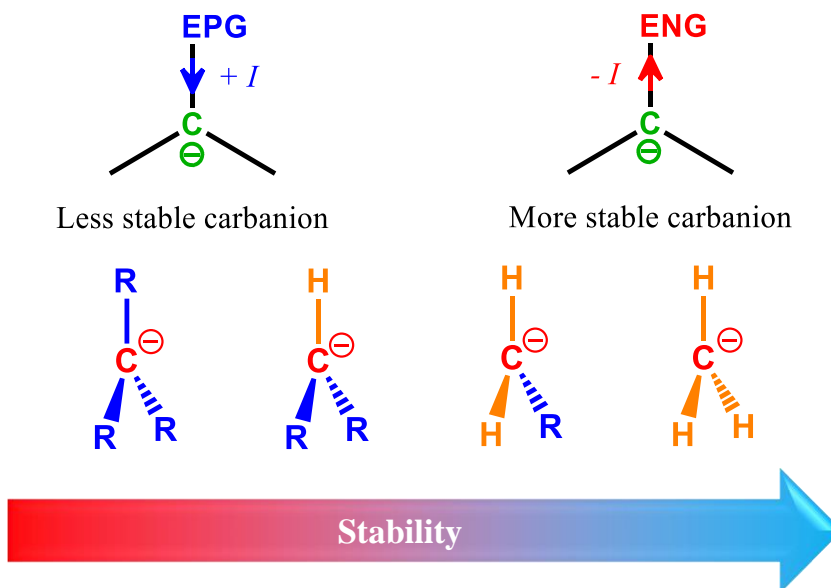
➲ ***Example***

Diethyl malonate forms a stable carbanion since the negative charge can be shared between the two carbonyl function.

In case of allylic and aromatic systems, the carbanionexhibits a positive mesomeric effect +*M*. In the example bellow, cyclopenta-2,4-dien-1-ide is stable because it is an aromatic ring where the negative charge is shared between five carbon atom.

Hybridization

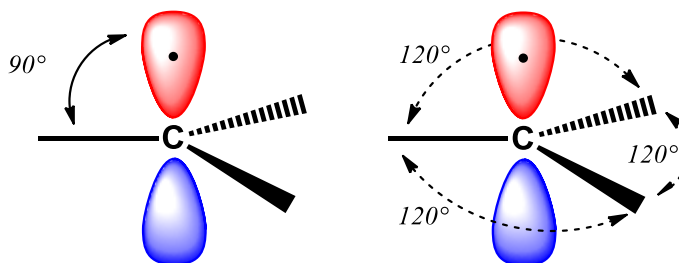
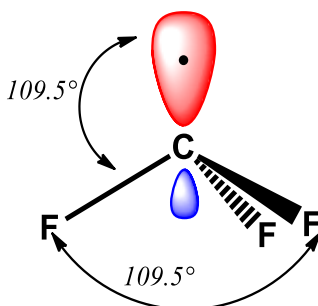
A carbanion species is the conjugate base form of an organic acid. As a result , the stability of a carbanion can also be measured through its acidity, which is affected by the hybridization of the carbon atom bearing the negative charge. In this case, hybridization plays a crucial role in determining whether the conjugate base is stable or not depending upon how close the negative charge is to the nucleus and therefore, acidity increases as **(s)** character increases. Consequently, sp hybridized carbanion is more stable than sp^2, which is more stable than sp^3.

Acid	Conjugate base “Carbanion”	Hybridization		pKa	Stability
$HC\equiv CH$ Acetylene	$HC\equiv C^{\ominus}$	sp		25	
		s: 50%	p: 50%		
$H_2C=CH_2$ Ethylene	$H_2C=\overset{\ominus}{C}H$	sp^2		44	
		s: 33.33%	p: 66.66%		
H_3C-CH_3 Ethane	$H_3C-\overset{\ominus}{C}H_2$	sp^3		≈ 50	
		s: 25%	p: 75%		

Inductive Effect

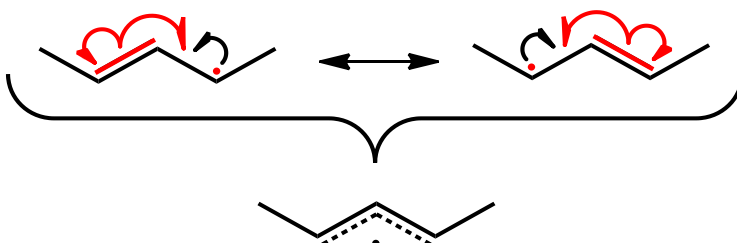
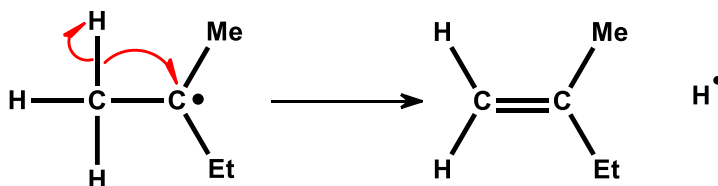
Electronegative groups stabilize carbanions through the negative inductive effect –*I*, which reduces the electron density of the carbanion. On the other hand, positive inductive effect +*I* of electropositive groups would provide more electron density to the carbanion making it less stable.

II. 1. 3. Free-radical Carbon

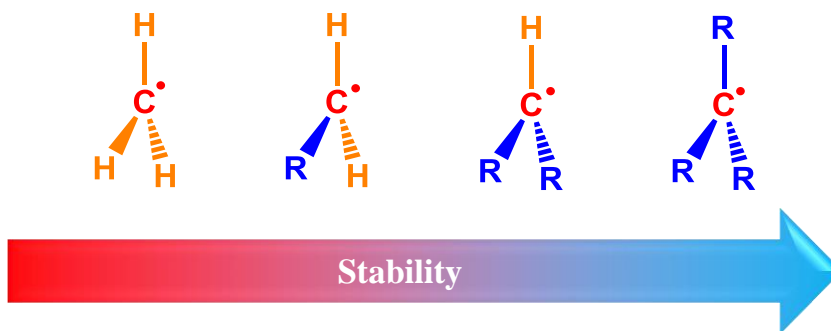
II. 1. 3. 1. Definition and Structure

Free radical carbons are sp^2 hybridized carbon atoms with seven valence electrons that possess one unpaired electron occupying the unhybridized p orbital. These species are short-living fragments and tend to be so reactive. In most cases, free radical carbon have a planar geometry for sp^2 hybridized radicals.

Nevertheless, trigonal pyramidal geometry can also be possible in some cases when the free radical carbon is sp^3 hybridized.

II. 1. 3. 2. Stability

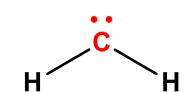
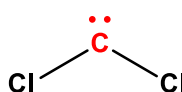
The same factors that stabilize carbocation can also be applied to free radical carbons.

Resonance

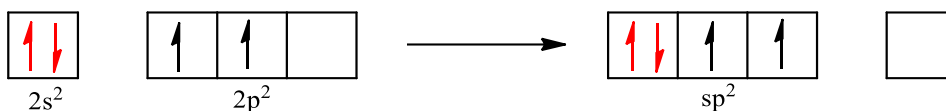
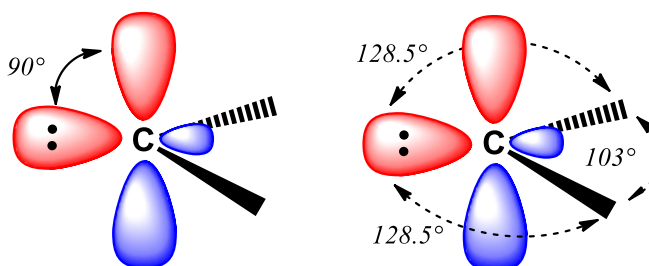
The single unshared electron of free radical carbon can participate in resonance in allylic and benzylic systems. In this case, the free radical carbon exhibits a positive mesomeric effect +*M*.

Hyperconjugation

Inductive Effect

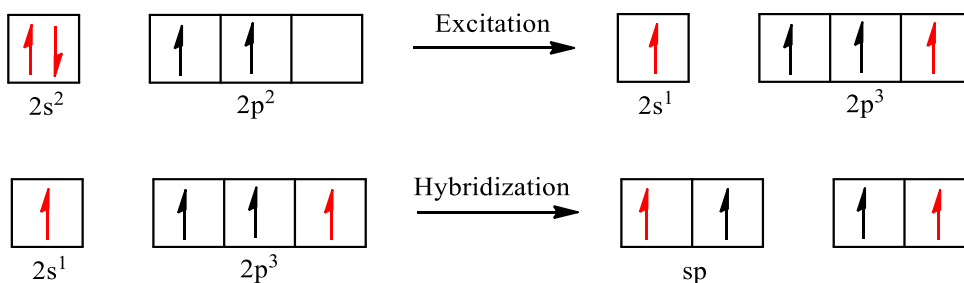
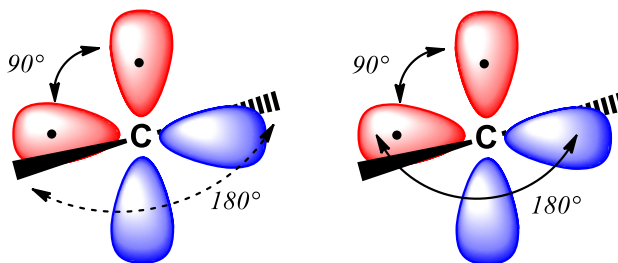
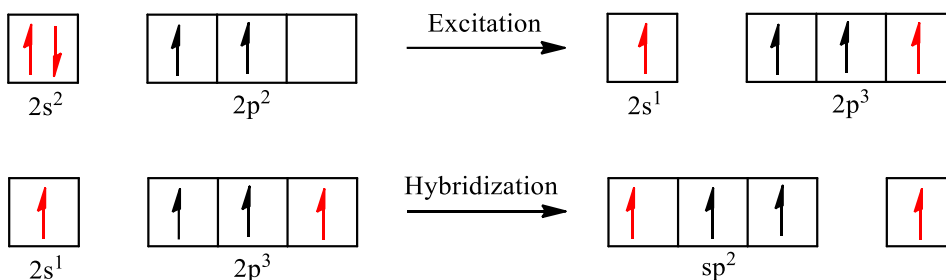
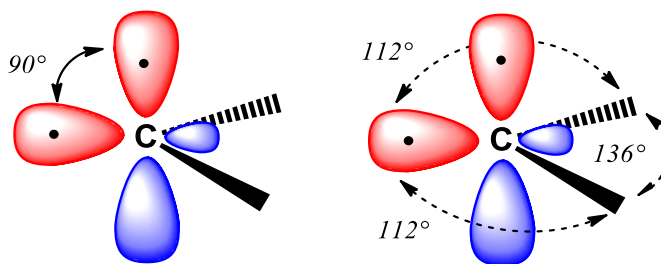
Carbon free radical stability increases with positive inductive effect $+I$. On the other hand, substituents that exhibit electron-withdrawing effect destabilize carbon free radicals.

II. 1. 4. Carbene

II. 1. 4. 1. Definition and Structure

Carbene compounds are highly reactive species that contain a bivalent carbon atom with two unshared valence electrons. These non-ionic fragments tend to have a very short lifetime, for example, the lifetime of formylcarbene H_2C: varies between 0.15 – 0.73 ns. Furthermore, carbenes are classified based on their electronic configuration into two categories singlet carbenes, and triplet carbenes.

Methylene; formylcarbene

Dichlorocarbene; dichloromethylene

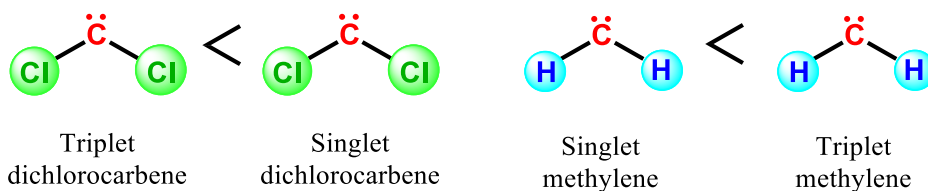
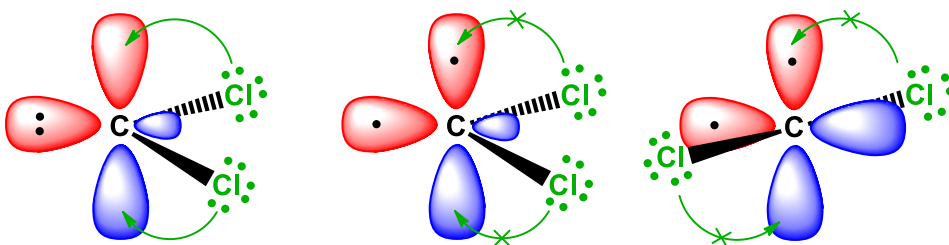
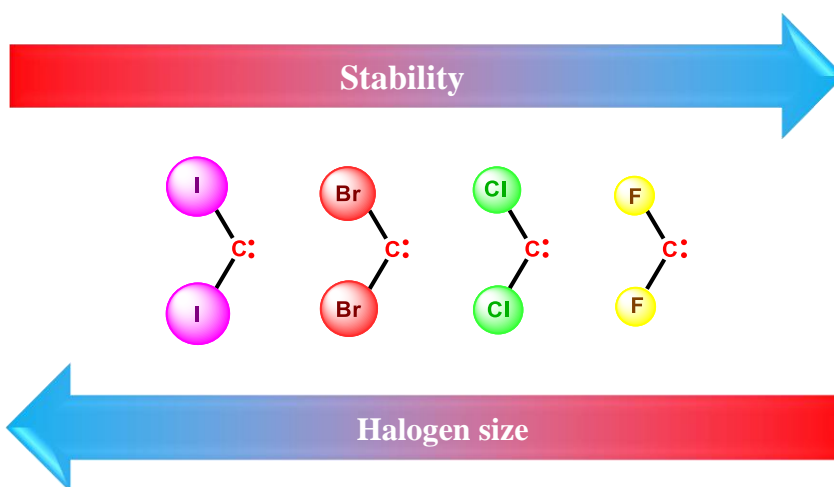
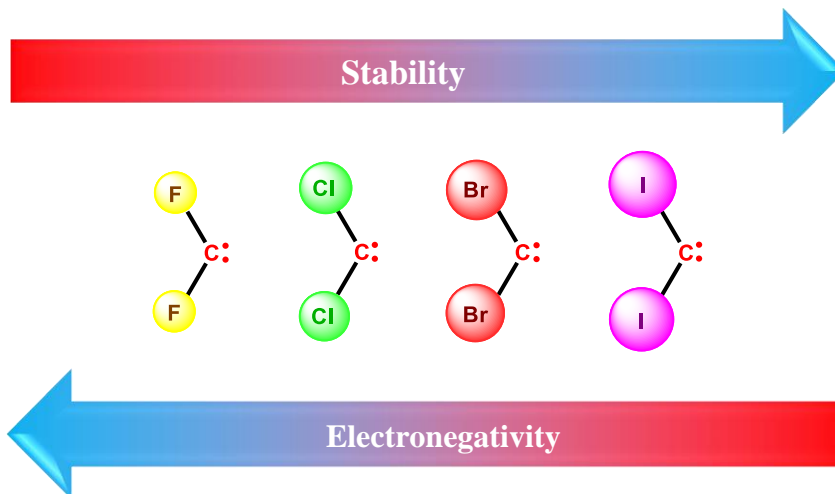
II. 1. 4. 2. Singlet Carbenes

Singlet carbenes are sp^2 hybridized carbons that have paired electrons and thus, they are often referred to as "spin-paired carbene". This particular type of carbenes have a spin equal to zero, which makes them diamagnetic species and they form when a saturated s orbital intermixes with two 2p orbitals resulting in an sp^2 hybridized carbon atom with a saturated sp^2 sub-shell.

Because they are sp^2 hybridized carbons, singlet carbenes have a planar bent geometry where the two unshared electrons occupy the sp^2 orbital and the angle between the two substituents is around 103° "singlet met hylene" while the remaining vacant p orbital is perpendicular on the plane. In addition, singlet carbenes tend to occur in aqueous media for they are not stable in a gaseous state.

II. 1. 4. 3. Triplet Carbene

Unlike singlet carbenes, triplet carbene s form from the excited state of electron orbitals when a single electron travels from the 2s orbital to the vacant p sub-shell orbital. In this case, the sub-shells can intermix in two different ways resulting in two different types of hybridizations. Nevertheless, in both cases, there would be two unpaired electrons, which makes triplet carbenes paramagnetic species with a spin equal to one. When the s orbital combines with only one p orbital, a linear triplet carbene forms with an sp hybridization.

In this case, the two unhybridized p orbitalscontain one electron each, and they are perpendicular on each other. Furthermore, the two substituents are 180° away from each other and they are perpendicular on both unhybridized p orbitals.

On the other hand, if the s orbital combines with two p orbitals, a bent triplet carbene forms with an sp^2 hybridization.

Here, one unshared electron occupies an sp^2 orbital while the other electron occupies a non-hybridized p orbital. In general, the angle between the substituents varies between 120° and 140°, for example, the angle between hydrogen atoms in triplet methylene is 136° *(steric interactions favor opening the angle somewhat from the ideal 120°).*

⊗Note: In most cases, triplet carbenes tend to have nonlinear geometry except for those with nitrogen, oxygen, or sulfur atoms.

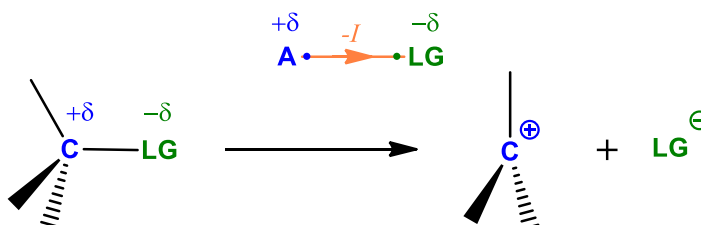
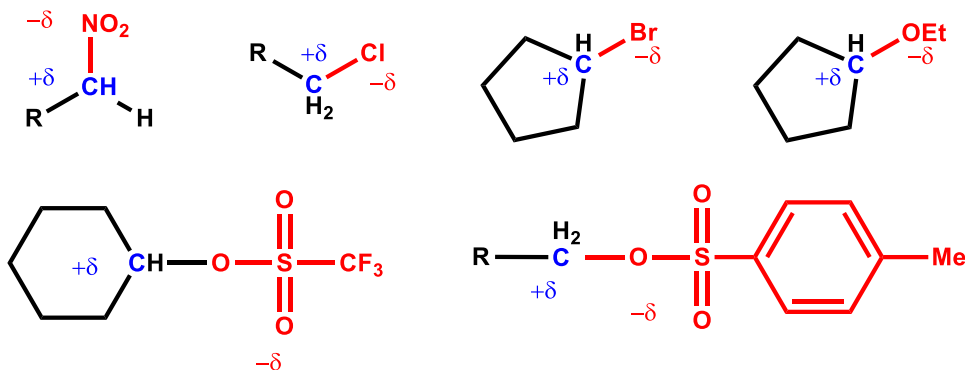
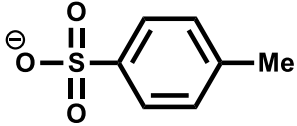
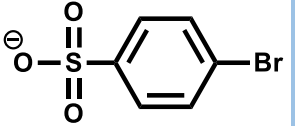
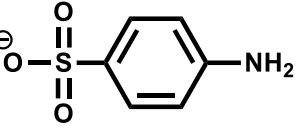
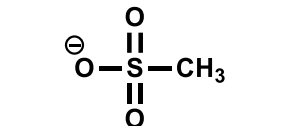
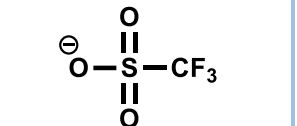
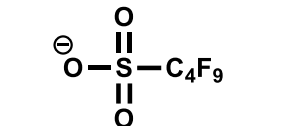
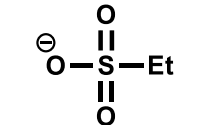
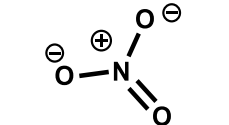
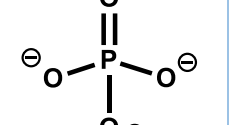
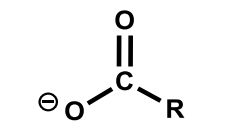
II. 1. 4. 4. Stability

Singlet carbenes are more stable when the two substituents are electronegative groups such as –Cl, –Br, or –O. In contrast, triplet carbenes are more stable when

the substituents are alkyl groups. For example, triplet methylene is more stable than its singlet analogue, whereas singlet dichlorocarbene is more stable than triplet dichlorocarbene due to the backbonding effect caused by the interactions between halogen lone pairs and the vacant p orbital.

The backbonding effect can only be observed in singlet carbenes because triplet ones do not have a fully vacant p orbital.

Moreover, the stability of singlet dihalocarbenes increases as the size of halogen decreases. This is because the p backbonding stabilizing effect is inversely proportional to atomic size.

For triplet dihalocarbenes, however, the opposite is true where stability increases as electronegativity decreases.

II. 2. Leaving Groups

Leaving groups can be a single atom or a group of atoms attached to a carbon atom of a substrate. They are essential to undergo certain organic reactions such as substitution and elimination reactons. As a leaving group departs from the substrate, it may or may not carry away the bonding electrons and therefore, leaving groups are classified into two groups; nucleofuges, and electrofuges.

II. 2. 1. Nucleofuges

The term nucleofuge refer to leaving groups that take away a full negative charge when they depart from the substrate. These particular type of leaving groups are electronegative groups (ENG) attached to a carbon atom. Due to their relatively higher electronegativity, they exercise an attractive inductive effect -*I* on the carbon atom to which they are directly attached. Consequently, a dipole-dipole moment with an electron deficiency on the least electronegative atom "carbon atom" forms. At the course of a chemical reaction, the bond connecting the nucleofuge to the substrate breaks heterolytically resulting in an anionic leaving group.

The following examples demonstrate how nucleofuges (red) pull the valence electrons of the carbon atom they are directly attached to resulting in a positive formal charge on these carbon atoms.

Sins nucleofuges have a negative charge, they can be considered as bases and therefore determining whether a species is a good nucleofuge or not depends upon its stability as a base, which can be affected by three factors; electronegativity, ionic size, and resonance. A good nucleofuge is a weak base. For example, iodine is a better nucleofuge than chlorine because iodine forms a weaker base “iodide” than chlorine “chloride”. The reason behind this is that iodide is more pol arizable than chloride due to its larger ionic size.

$HO^- < F^- << Cl^- < Br^- < I^- < MsO^- < TsO^-$

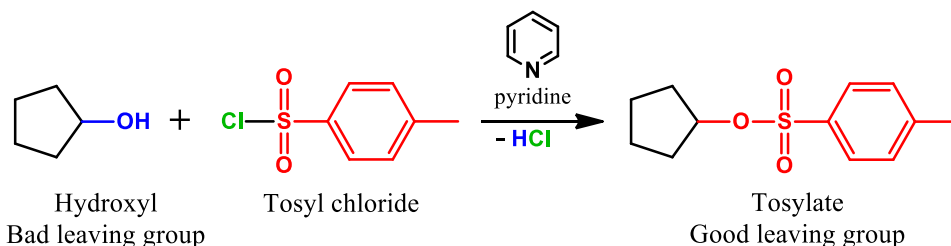
Hydroxyl group is a very bad leaving group because it is a strong base. As a result, it is usually converted to a sulfonic ester which is an excellent leaving group by treating the substrate with the appropriate sulfonic chloric acid. In the example below, hydroxyl group is converted into tosylate by reacting cyclopenanol with tosyl chloride under basic condition “pyridine”.

pyridine

- HCl

Hydroxyl
Bad leaving group

Tosyl chloride

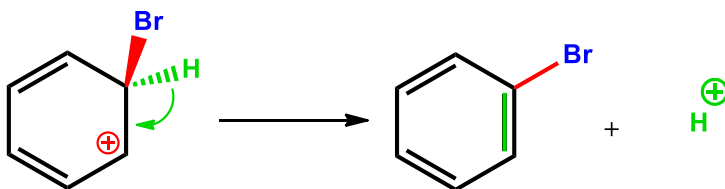
Tosylate
Good leaving group

The following table represents a list of some common nucleofuges in organic chemistry.

Cl^-	Br^-	I^-	H_2O	NH_3	NR_3
Chloride	Bromide	Iodide	Water	Ammonia	Amines

OTs Tosylate	**OBs** Brosylate	**ONs** Nosylate
OMs Mesylate	**OTf** Triflate	Nonaflate

Tresylate	Nitrate	Phosphate	Carboxylates

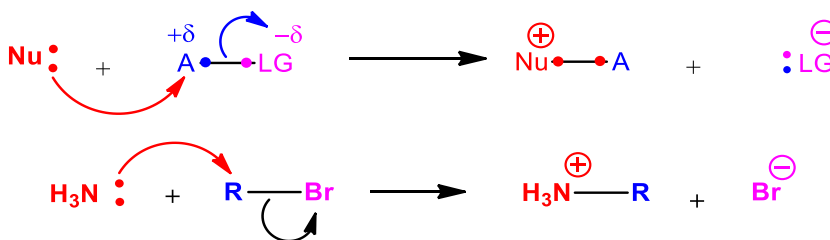
II. 2. 2. Electrofuges

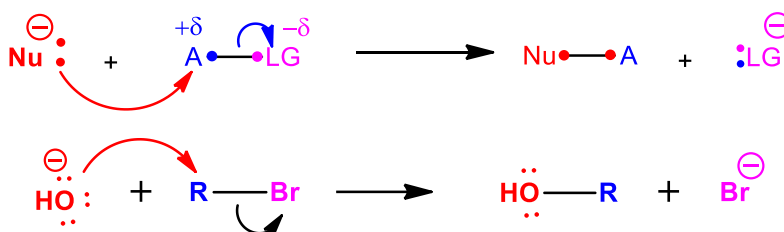
By definition, an electrofuge is a leaving group that does not carry away the bonding electron when it departs from the substrate. This type of leaving groups are mainly observed in electrophilic aromatic substitution reactions.

II. 3. Nucleophiles

Nucleophiles are chemical species with high electron density; they can be neutral molecules with a lone pair, molecular anions, ions with negative charge, or molecules with at least one pi bond. The term **nucleo–** came from the Latin word *nucleus* which refers to the nucleus of atoms. On the other hand, the suffix **–phile** is derived from the Greek word *philos*, which means lover, and thus, the term nucleophile signifies *nucleus lover*. When undergoing certain chemical reactions, the nucleophile attacks an electron deficient species such as a carbocation or a partially positive carbon atom and form a new covalent bond with it.

II. 3. 1. Types of Nucleophiles

II. 3. 1. 1. Neutral Nucleophiles

Usually represented by Nu**:** or Nu, a neutral nucleophile with nonbonding lone pair can form a covalent bond with carbon atoms bonded to a nucleofuge. In this case, the nucleophile will provide its lone pair electrons and create a new covalent bond with this carbon atom.

II. 3. 1. 2. Charged Nucleophiles

Represented by Nu⁻, anions and molecular anions can also create a covalent bond with carbon atoms. In fact, they are more reactive than neutral nucleophiles due to their higher electron density.

II. 3. 2. Nucleophilicity

The term nucleophilicity describes the strength of a nucleophile. The more available the elec trons, the stronger the nucleophilic. In general, nucleophilicity depends upon four factors:

Charge

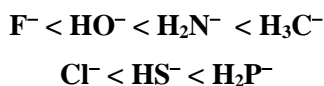
Anionic nucleophiles are always stronger than their neutral forms.

$$H_2O < HO^- \quad H_3N < H_2N^- \quad MeSH < MeS^-$$

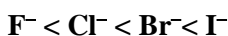
Electronegativity

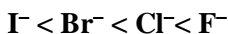
If the nucleophiles belong to the same row of the periodic table, n ucleophilicity decreases with the electronegativity of the nucleophilic atom.

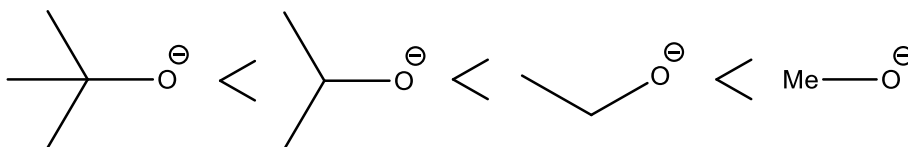
$$F^- < HO^- < H_2N^- < H_3C^-$$

$$Cl^- < HS^- < H_2P^-$$

Solvent

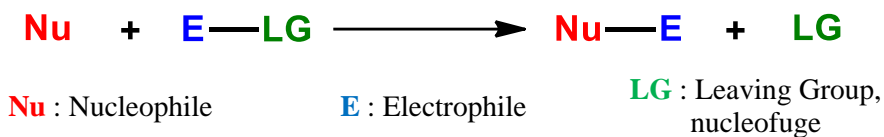
The strength of nucleophiles varies depending upon the solvent in which they are . In a protic solvent, nucleophilicity increases with basicity. The stronger the congregate base, the stronger the nucleophile.

$$F^- < Cl^- < Br^- < I^-$$

On the other hand, in aprotic solvents, nucleophilicity increases with electronegativity of the nucleophilic atom.

$$I^- < Br^- < Cl^- < F^-$$

Steric hindrance

Nucleophilicity decreases with the steric hindrance.

II. 4. Electrophiles

Electrophiles are chemical species with a vacant orbital; this property make them susceptible of accepting an electron pair from another species with high electron density and form a covalent bond with them. Since they are electron acceptors, electrophiles are considered to be Lewis acids where most of them are positively charged.

Nu : Nucleophile **E** : Electrophile **LG** : Leaving Group, nucleofuge

III. Reaction Mechanisms

III. 1. Substitution Reactions

In organic chemistry, substitution reactions are reactions where substituents get replaced by other species. These reactions are categorized into three main classes depending upon the reaction conditions and reagents involved.

1. Free-radical substitution reactions.
2. Nucleophilic substitution reactions.
3. Electrophilic substitution reactions.

III. 1. 1. Free-radical Substitution Reactions

Free radical substitution is a chemical reaction that involves free radical species in which one or more hydrogen atoms of an organic compound are replaced by another species. This reaction occurs under the influence of UV light, significant amount of heat energy, or radical initiators. Halogenation of hydrocarbons is one of the most important reactions in organic chemistry, it is performed via free radical substitution and it is characterized by three steps; initiation, propagation, and termination.

III. 1. 1. 1. Alkanes Halogenation

Alkanes are saturated hydrocarbons that contain only carbon and hydrogen atoms connected together with single covalent bonds. In general, these compounds are considered unreactive since they lack reactive functional groups or unsaturation. Nevertheless, alkanes can undergo some reactions such as combustion "destruction of alkanes”, pyrolysis “cracking”, reactions with magic acids such as HF-SbF_5 and FSO_3H-SbF_5, and free radical halogenation. This latter is the most commonly used reaction and it consists in transforming the unreactive alkane into a more reactive substance “alkyl halides, alkyl dihalides, alkyl trihalides, and alkyl tetrahalides.

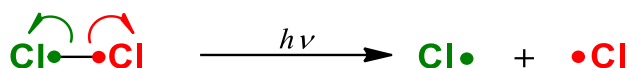
Mechanism

Free radical halogenation of alkanes is a chain reaction that passes through three stages.

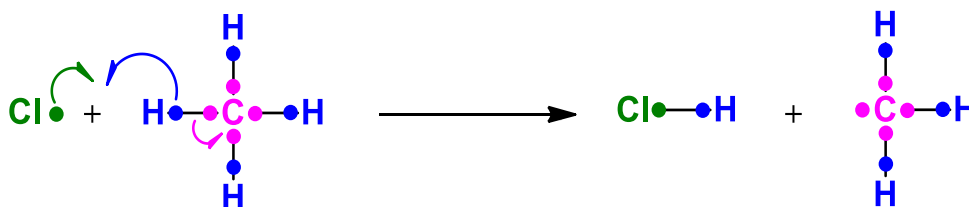
Initiation

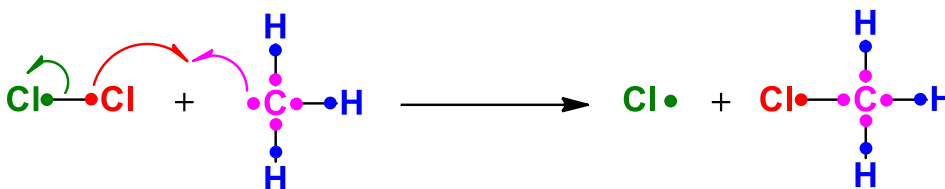
The first step of halogenation requires UV light or sufficient heat energy in order to generate free radical halogens from dihalogen molecules. However, once free radicals are formed, the reaction is self-sustaining and UV light or heat are no longer necessary. For example, when UV light radiation penetrates dichlorine molecule, the covalent bond connecting the two chlorine atoms breaks in such a

way where each chlorine atom would carry away one unshared electron. This process creates, as a result, two free radicals of chlorine.

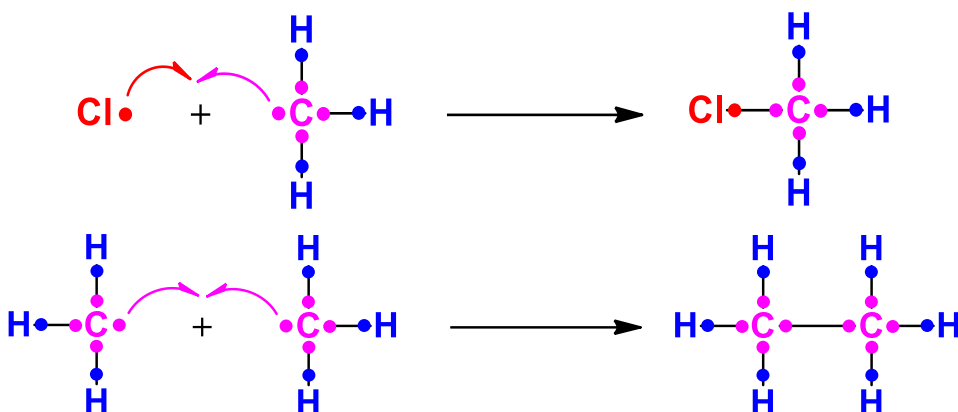
$$Cl\bullet\!-\!\bullet Cl \xrightarrow{h\nu} Cl\bullet + \bullet Cl$$

Propagation

The next step is called propagation where free radical halogens formed in the first step react with the substrate "methane". At this point, two types of reactions might occur; the first one is the reaction of chlorine free radical with methane in which chlorine grabs one hydrogen atom from methane resulting in the formation of two new species; hydrogen chloride and methyl free radical.

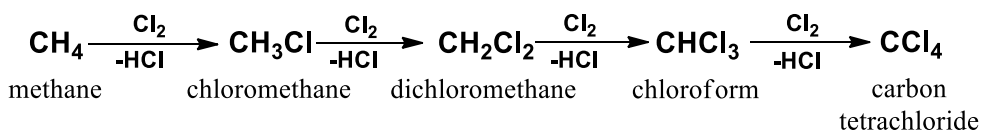
$$Cl\bullet + H\!-\!CH_3 \longrightarrow Cl\!-\!H + \bullet CH_3$$

The second reaction proceeds in a similar way but in this case with the methyl free radical and another molecule of dichlorine, which produces a chloromethane molecule and a new chlorine free radical.

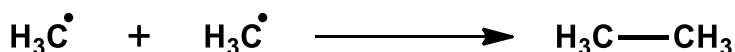
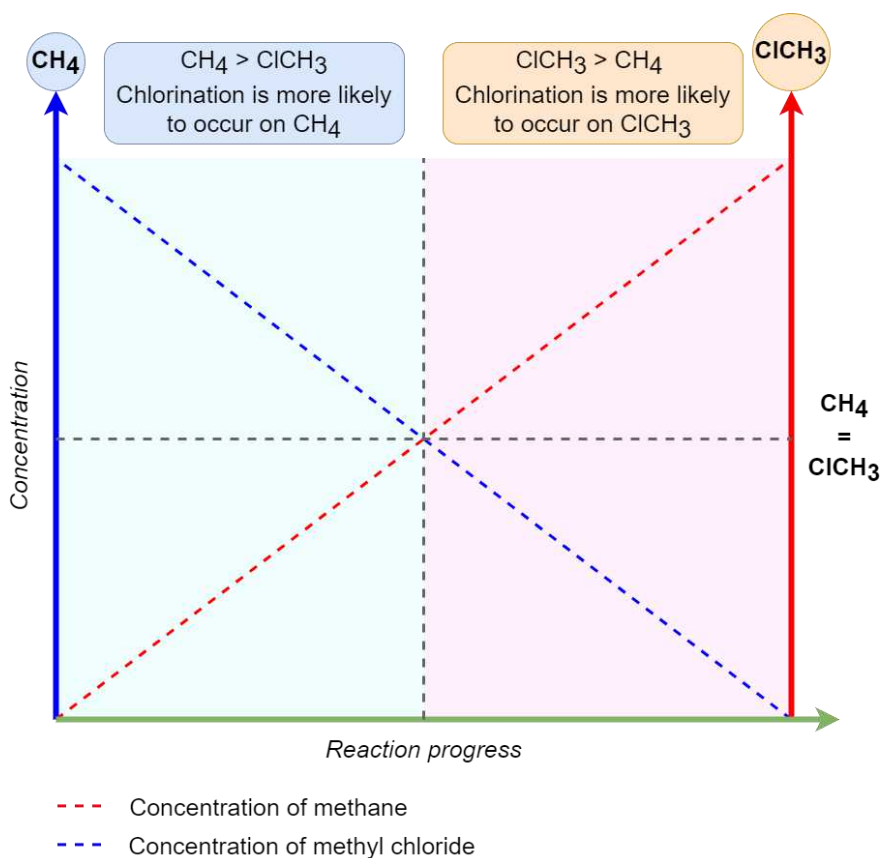
$$Cl\!-\!Cl + \bullet CH_3 \longrightarrow Cl\bullet + Cl\!-\!CH_3$$

Termination

In the final step, free radicals combine and form new molecules. In this case, either two chlorine free radicals combine to give dichlorine, a chlorine free radical combines with alkyl radical, or two alkyl radicals combine to form a higher alkane.

$$Cl\bullet + \bullet Cl \longrightarrow Cl\!-\!Cl$$

Control of Free Radical Halogenation

Free radical halogenation of alkanes does not usually stop at one substitution. If it is not controlled, a mixture of all potential products would be obtained. For example, chloromethane can undergo further substitution reaction and produces dichloromethane. Similarly, dichloromethane can also reacts with other dichlorine molecules and form chloroform then carbon tetrachloride.

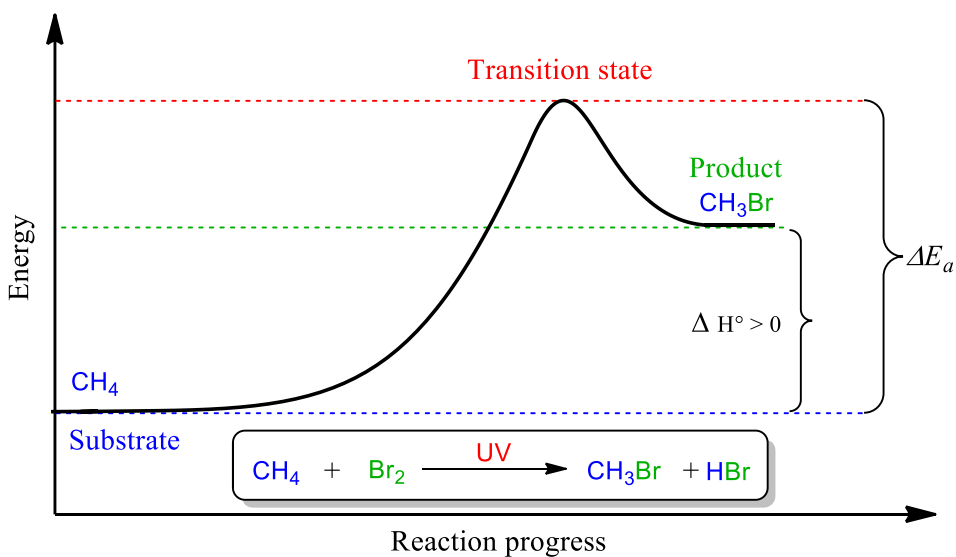
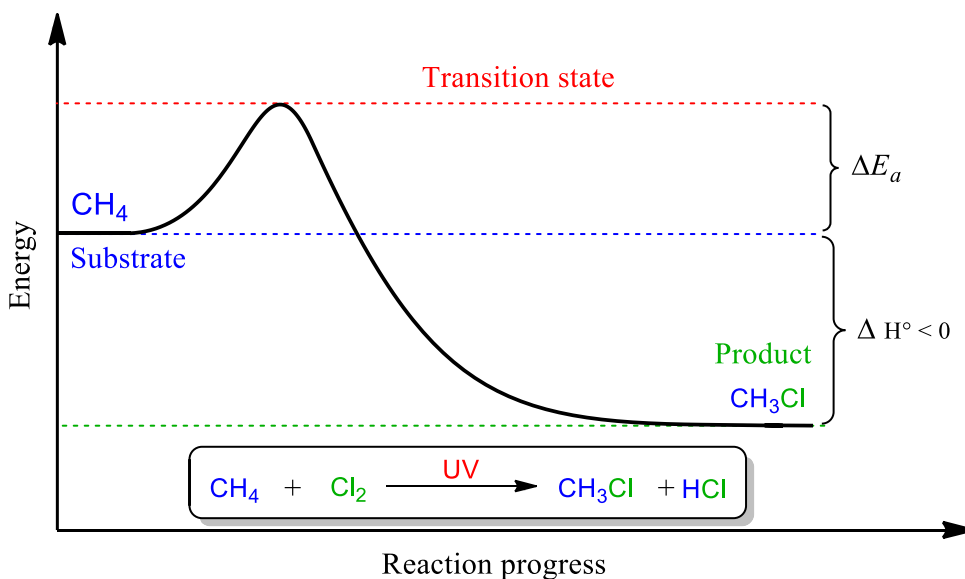
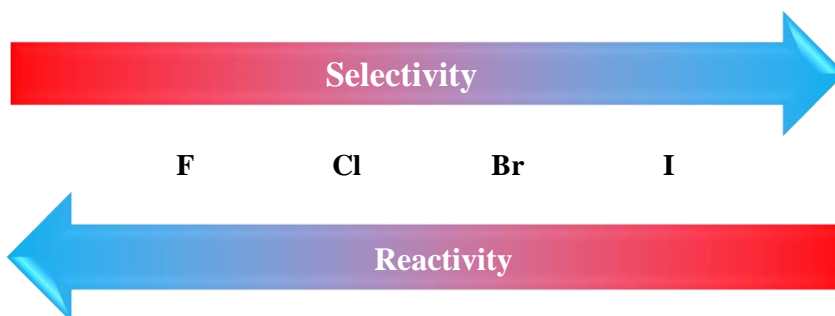
$$\underset{\text{methane}}{CH_4} \xrightarrow[-HCl]{Cl_2} \underset{\text{chloromethane}}{CH_3Cl} \xrightarrow[-HCl]{Cl_2} \underset{\text{dichloromethane}}{CH_2Cl_2} \xrightarrow[-HCl]{Cl_2} \underset{\text{chloroform}}{CHCl_3} \xrightarrow[-HCl]{Cl_2} \underset{\text{carbon tetrachloride}}{CCl_4}$$

Moreover, free radical carbon species can also react with one another to form new C–C covalent bonds.

$$H_3C^{\bullet} + H_3C^{\bullet} \longrightarrow H_3C{-}CH_3$$

This phenomenon happens because as more methane molecules turn into methyl chloride, the concentration of methane decreases and as a result, methyl chloride molecules produced would compete with the remaining methane molecules. In this case, chlorine free radicals are more likely to react with methyl chloride and form dichloromethane than to react with methane. The diagram below demonstrate how the concentration of methane affects the probability of further halogenations.

⊗ Note: This diagram is only to visualize the probability of dichlorination of methane in 1:1 ratio.

In order to maximize the amount of the desired product, specific procedure can be applied, which restrict further halogenation. For example, using excess amount of methane at the course of the reaction would increase methyl chloride yielding as the probability of further chlorination of methyl chloride gets lower. In addition, since haloalkanes have different physical properties than alkanes, it may be possible to separate the products from the reaction medium through distillation or other separation methods.

Relative Reactivity and Selectivity of Halogens

Although both of bromine and chlorine undergo free radical halogenation, they do not behave in the same way and give different yields for the same products. This differentiation is related to the relative selectivity of each halogen. For instance, methane reacts with bromine in a similar way to chlorine and produces bromomethane, methylene bromide, bromoform, and carbon tetrabromide.

However, in contrast to chlorination, bromination is a slower reaction due to stability of free radical bromine, which is maintained bythe bromine polarizability. As a result , more energy mu st be provided to bromine in order to surpass the activation energy barrier and generate bromine free radicals. The diagrams below illustrates the difference between chlorination and bromination of methane. The activation energy of chlorination is smaller than the activation energy of bromination. In addition, chlorinat ion of alkanes is an exothermic reaction where the products are more stable than the starting material. In contrast, bromination is an endothermic reaction that requires more energy in order to proceed.

Unlike bromine and chlorine, fluorine reacts vigorously with methane that even in the dark and at room temperature, fluorination must be carefully controlled. Th e reason behind this is that fluorine has a higher reactivity than all the other halogens due to its higher electronegativity and small size. Iodine, on the other hand, does not react with methane because of its higher stability.

When performing a halogenation reaction, different products may be obtained with different yields. This depends upon the selectivity of the halogen involved and the number of available hydrogen atomsthat can be replaced Reactivity and selectivity are inversely proportional, the more reactive a reagent, the less selective. Bromine has a higher selectivity than chlorine. As result, it tends to add to the most substituted carbon atom. In contrast, chlorine is less selective that all potential products are produced with significant amount. In theory, it is possible to predict the yield of all possible isomers using the following formula:

$$P_i\% = 100\frac{n\,H_i\,R_i}{\sum_i n\,H_i\,R_i}$$

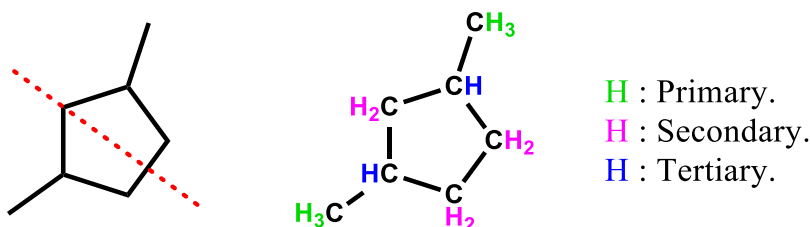
- P_i: Yield of product i.
- Nh_i: Number of hydrogen atoms of type i.
- R_i: Reactivity factor for type i.
- Σ_i: Sum of all types.
- Table : Reactivity factors for chlorine and bromine.

Hydrogen	Primary H	Secondary H	Tertiary H
Cl	1	3.9	5.2
Br	1	82	1640

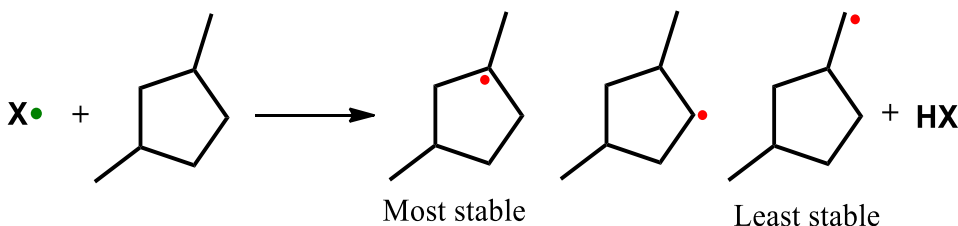
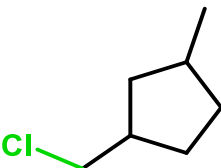
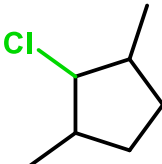
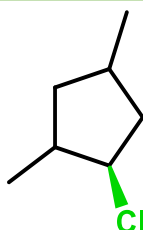
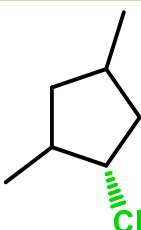
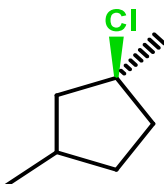
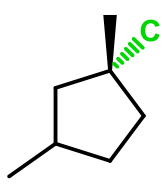
➲ ***Example***

Comparison between monochlorination and monobromination of dimethylcyclopentane.

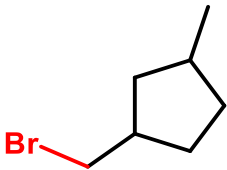
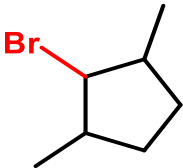
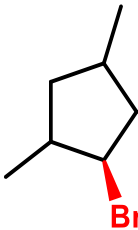
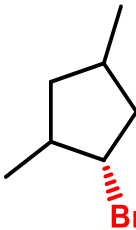
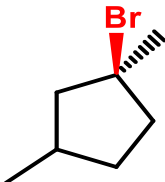
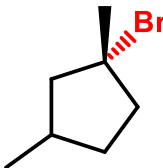
Dimethylcyclopentane is a symmetrical molecule that contains6 primary hydrogen atoms, 6 secondary hydrogen atoms, and 2 tertiary hydrogen atoms.

H : Primary.
H : Secondary.
H : Tertiary.

At the propagation step, a hydrogen atom would be abstracted from the substrate, which leads to the formation of a radical carbon intermediate. In this case, there would be three potential radical carbon intermediate where the most stable is the one formed when abstracting a tertiary hydrogen atom. On the other hand, primary radical carbon intermedia te are the least stable and ther efore, the probability of chlorine to add on this carbon is the lowest.

X• + → + HX

Most stable Least stable

For primary hydrogens

$$P_i\% = 100\times\frac{6\times1}{6\times1 + 6\times3.9 + 2\times5.2} = 3.35\%$$

For secondary hydrogens

$$P_i\% = 100\times\frac{6\times3.9}{6\times1 + 6\times3.9 + 2\times5.2} = 41.34\ \%$$

For tertiary hydrogens

$$P_i\% = 100\times\frac{2\times5.2}{6\times1 + 6\times3.9 + 2\times5.2} = 55.12\ \%$$

Notice that both stereoisomers form when the halogen adds to a chiral carbon. The reason behind this is that free radical carbons have a planar geometry, which permits the addition of halogens on either sides and therefore, both stereoisomers may form.

In case of monobromination, 1 -bromo-1,3-dimethylcyclopentane would predominate over the other isomers (95.21%) since bromine preferentially adds to the most substituted free radical carbon. The other products might be observed but they would have an insignificant yields “0.019% and 4.46%.”

III. 1. 1. 2. Allylic and Benzylic Halogenation

Unlike saturated hydrocarbons, allylic compounds may follow different pathways depending upon reaction conditions. At high concentration of halogens, allylic compounds undergo electrophilic addition (*page 132*) rather than free radical substitution reaction. However, when the concentration of halogens is controlled and kept low, free radical s ubstitution reaction takes place whereby the allylic hydrogen atom gets replaced by the halogen.

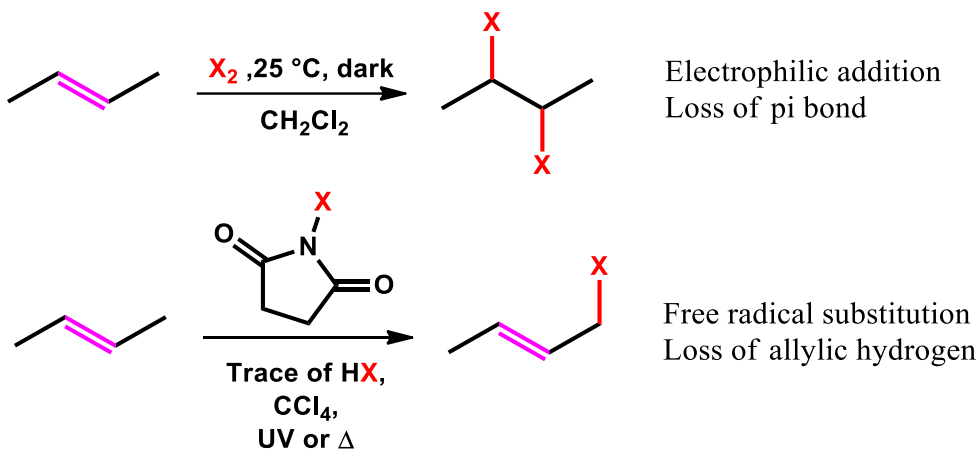
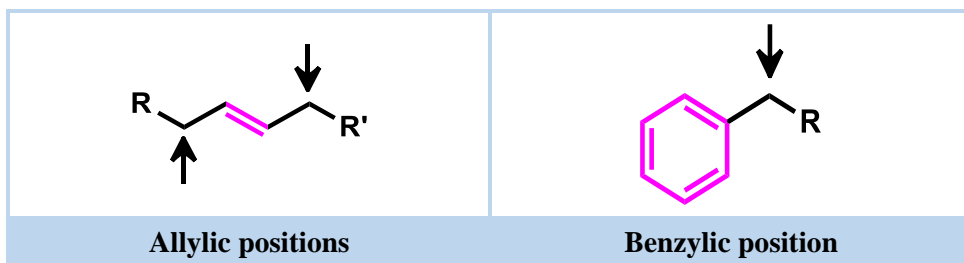
Allylic positions	Benzylic position

X_2 ,25 °C, dark

CH_2Cl_2

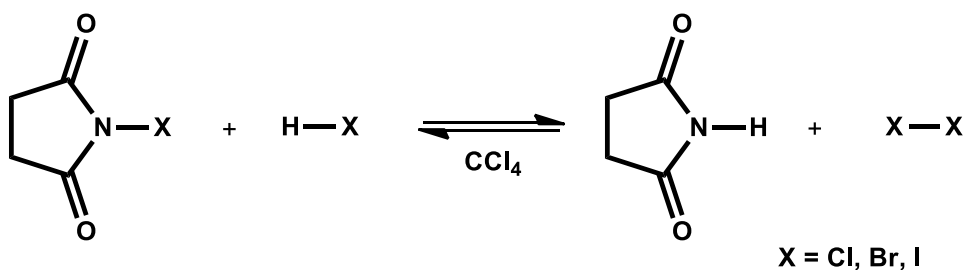
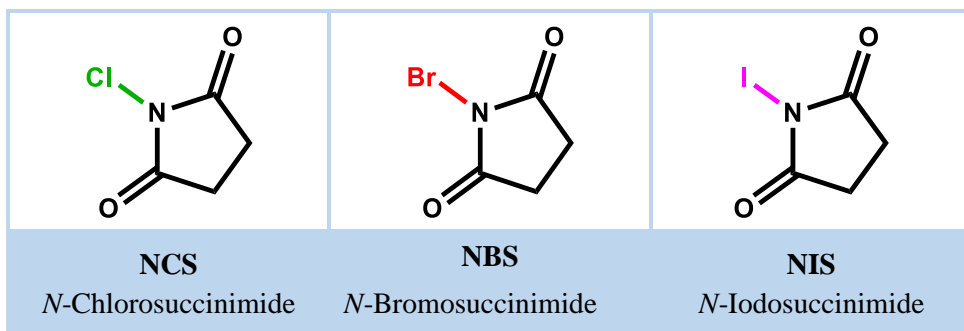
Electrophilic addition
Loss of pi bond

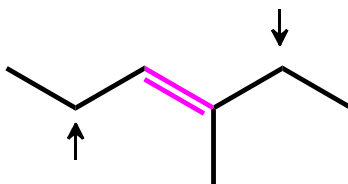
Trace of HX, CCl_4, UV or Δ

Free radical substitution
Loss of allylic hydrogen

N-halosuccinimides are halogen source reagents typically used in allylic and benzylic halogenation reactions in order to avoid electrophilic addition to the double bond. In this reaction, a stoichiometric amount of *N*-halosuccinimide is required along with a small amount of the corresponding hydrogen halide to produce a low concentration of the corresponding dihalide making free radical substitution reaction possible.

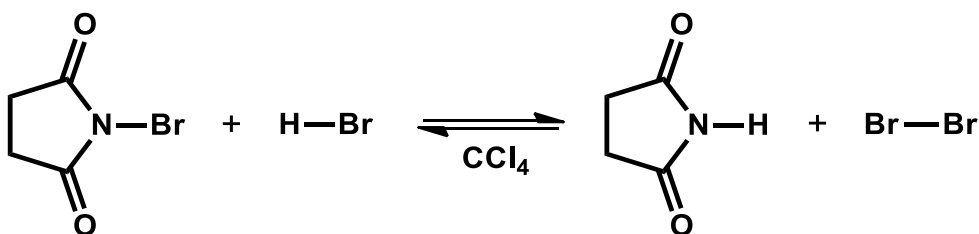
CCl_4

X = Cl, Br, I

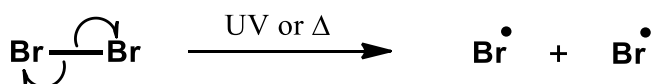
NCS	NBS	NIS
N-Chlorosuccinimide	*N*-Bromosuccinimide	*N*-Iodosuccinimide

Mechanism

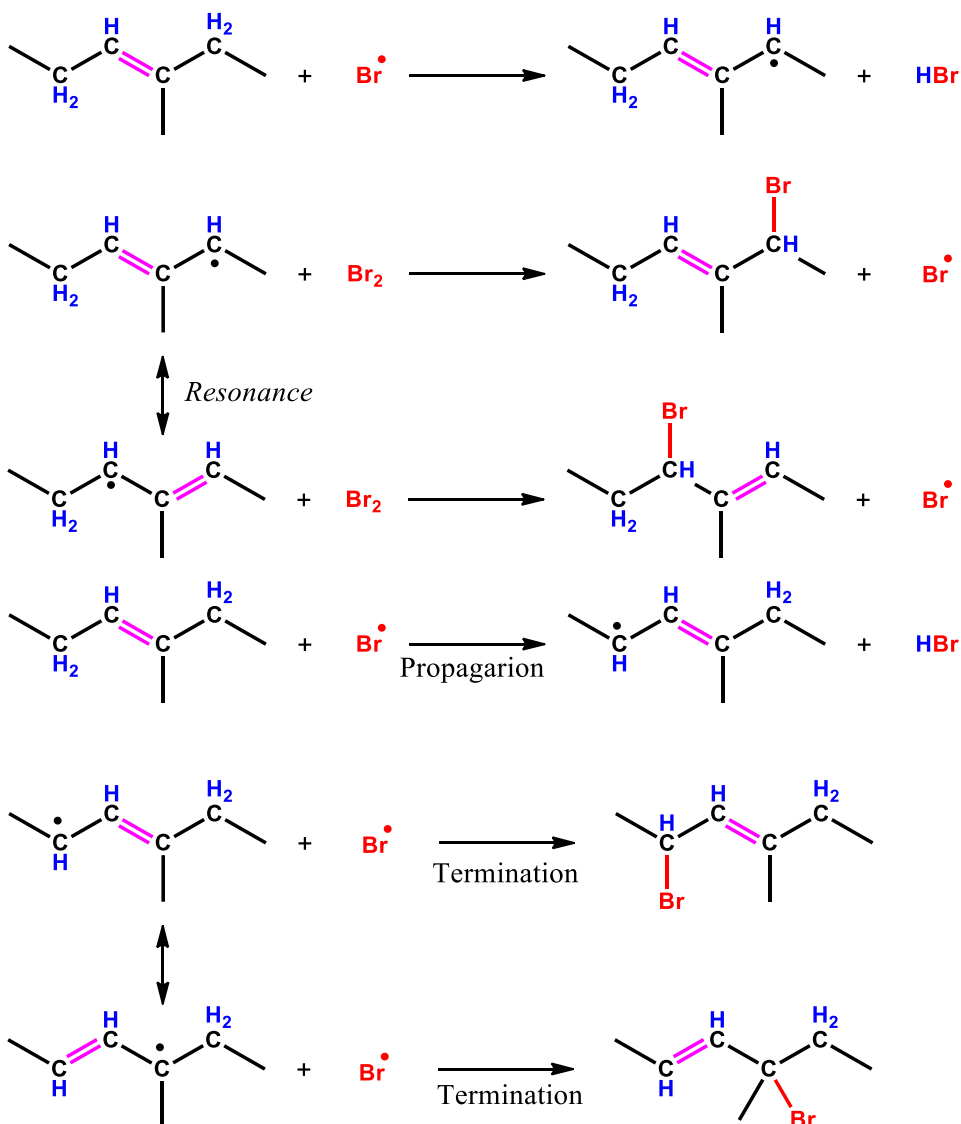
Allylic bromination reaction is also known as *Wohl-Ziegler* reaction, which consists in converting olefins into olefin bromides. The reaction mechanism is similar to regular alkanes halogenation except that *Wohl-Ziegler* reaction requires NBS to keep bromine concentration adequate for allylic substitution.

Production of dibromine

This is a reversible reaction where NBS reacts with HBr to produce dibromine and succinimide. This process is repeated whenever new HBr is available.

$$\text{N–Br} + \text{H–Br} \underset{CCl_4}{\rightleftharpoons} \text{N–H} + \text{Br–Br}$$

Initiation

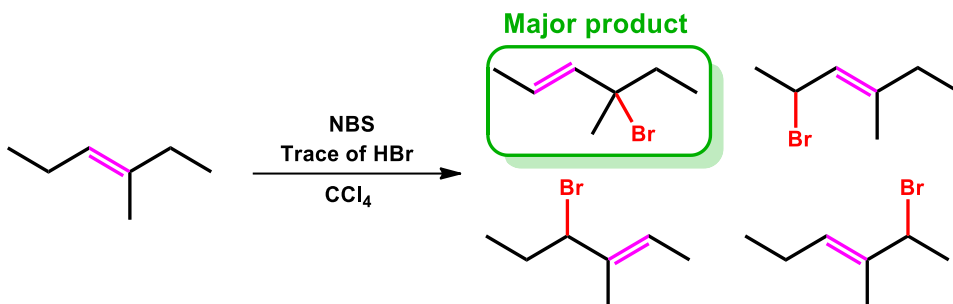
Under UV light or at high temperature, the dibromine formed would give two bromine free radicals upon homolytic fission of the covalent bond.

$$\text{Br–Br} \xrightarrow{\text{UV or } \Delta} \text{Br}^{\bullet} + \text{Br}^{\bullet}$$

Propagation and Termination

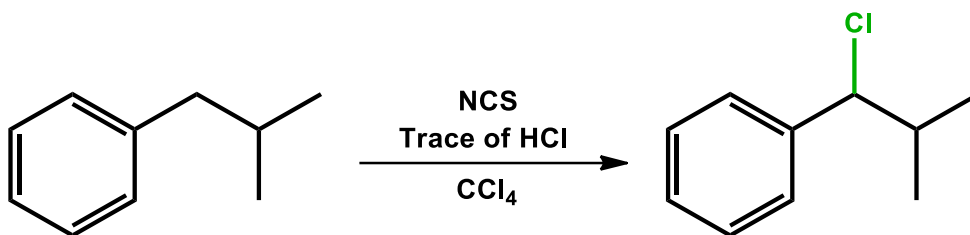
When free radical carbon forms on the allylic position, resonance becomes possible and as a result, bromine can add on either radical allylic carbon atoms.

Moreover, although this reaction may produce four compounds , only one product would be predominant over the others because bromine preferentially adds to the most substituted allylic radical.

Major product

NBS
Trace of HBr
CCl_4

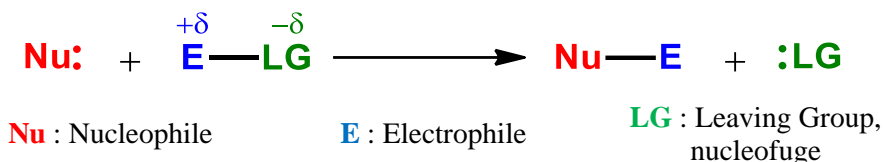
Br Br Br Br

Under UV radiation, at high temperature, or with radical initiators, benzylic compounds undergo free radical substitution reactions on the benzylic position when they are treated withNCS and HCl in CCl_4. Nevertheless, this reaction is also possible with Cl_2 and UV light.

NCS
Trace of HCl
CCl_4

Cl

III. 1. 2. Nucleophilic Substitution Reactions

Nucleophilic substitution reactions are one of the fundamental chemical reactions in organic chemistry. They are characterized by the replacement of a nucleofuge with a nucleophile.

$$\mathbf{Nu:} + \overset{+\delta}{\mathbf{E}}-\overset{-\delta}{\mathbf{LG}} \longrightarrow \mathbf{Nu}-\mathbf{E} + \mathbf{:LG}$$

Nu : Nucleophile **E** : Electrophile **LG** : Leaving Group, nucleofuge

Furthermore, depending upon the substrate type, nucleophilicsubstitution reactions are classified into two main categories; nucleophilic aliphatic substitutions, and aromatic nucleophilic substitutions.

III. 1. 2. 1. Nucleophilic Aliphatic Substitution Reactions

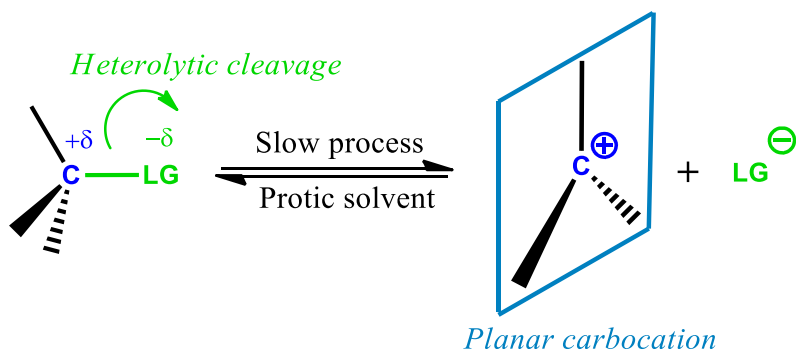
Nucleophilic aliphatic reactions are subdivided into two types of r eactions: unimolecular nucleophilic substitution reaction, and bimolecular nucleophilic substitution reaction. Although both reactions involve the same process "the displacement of leaving group", each type requires specific conditions in order to proceed.

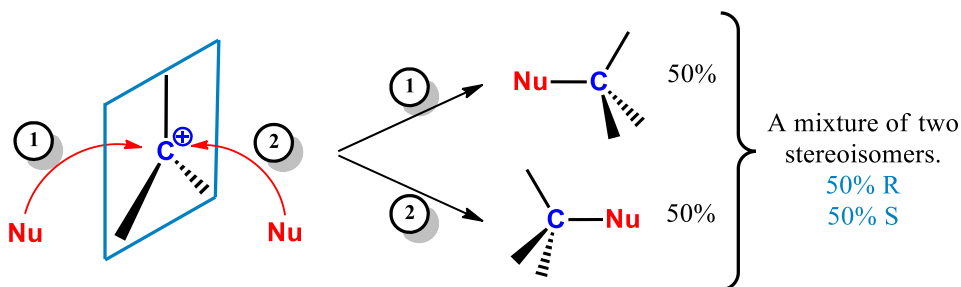
Unimolecular Nucleophilic Substitution Reactions S_N1

S_N1 Mechanism

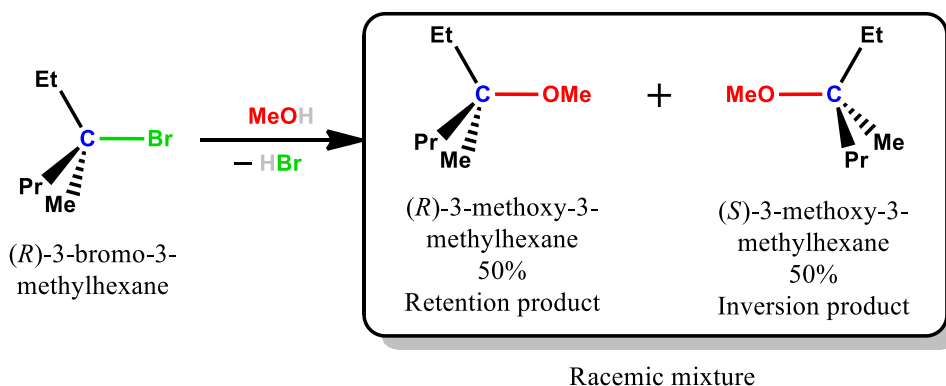
S_N1 reaction proceeds in two steps and involves a carbocation intermediate.

Step One

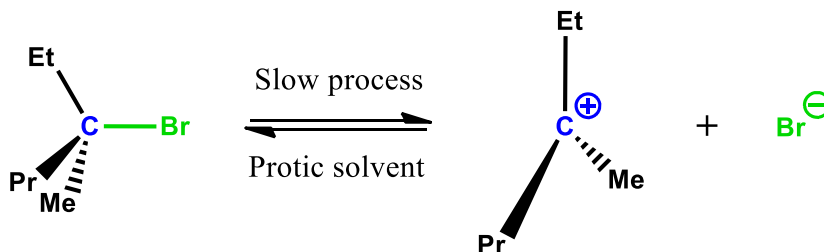
The first step is a slow process characterized by the heterolytic fission of the C–LG bond, which leads to the formation of a planar carbocation. This step may or may not be reversible.

Step Two

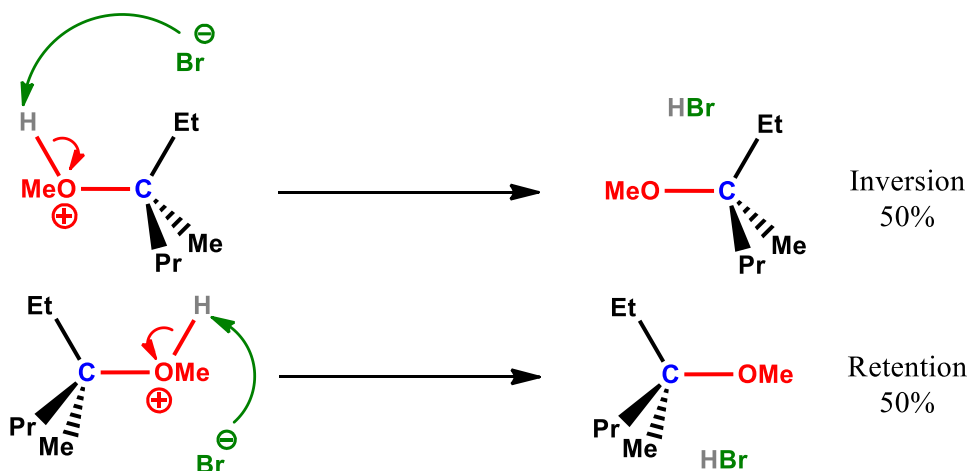
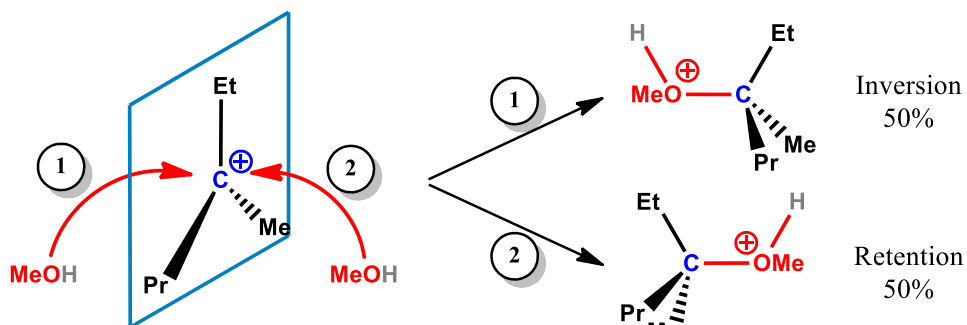
The second step, on the otherhand, is a fast process wherebythe nucleophile attacks the planar carbocation from either sides creating a new covalent bond with it. If this carbocation is formed from a chiral carbon, the reaction will give a mixture of two stereoisomers. This particular propriety makes S_N1 reaction a **non-stereoselective** reaction.

➲ ***Example 1:***

If the substrate contains only one chiral center, S_N1 reaction would lead to an enantiomeric mixture "racemic mixture", which is **optically inactive**.

Racemic mixture

Step one

Formation of carbocation intermediate.

Et C Br Pr Me — Slow process / Protic solvent ⇌ Et C⊕ Me Pr + Br⊖

Step two

Attack of the nucleophile.

➲ ***Example 2:***

If the substrate contains more than one chiral center, the reaction outcome would be a diastereoisomeric mixture. In this case, the mixture obtained is **optically active**.

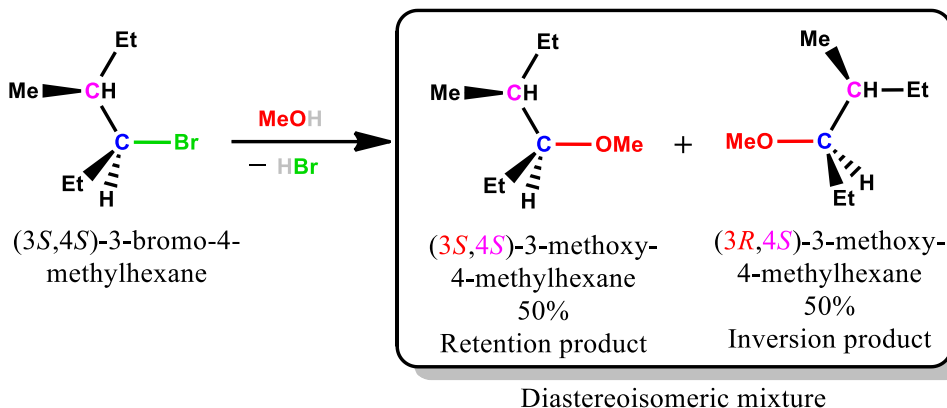
(3*S*,4*S*)-3-bromo-4-methylhexane

MeOH

− HBr

(3*S*,4*S*)-3-methoxy-4-methylhexane
50%
Retention product

(3*R*,4*S*)-3-methoxy-4-methylhexane
50%
Inversion product

Diastereoisomeric mixture

Carbocation Rearrangement (hydride, methyl, and aryl shifts)

As mentioned before, carbocations tend to acquire a more stable state by delocalizing the positive charge to a more substituted carbon atom via 1,2-shift. In this example, the secondary carbocation intermediate can rearrange into a tertiary carbocation via hydride shit, which will then get captured by the nucleophile “MeOH”.

Secondary carbocation

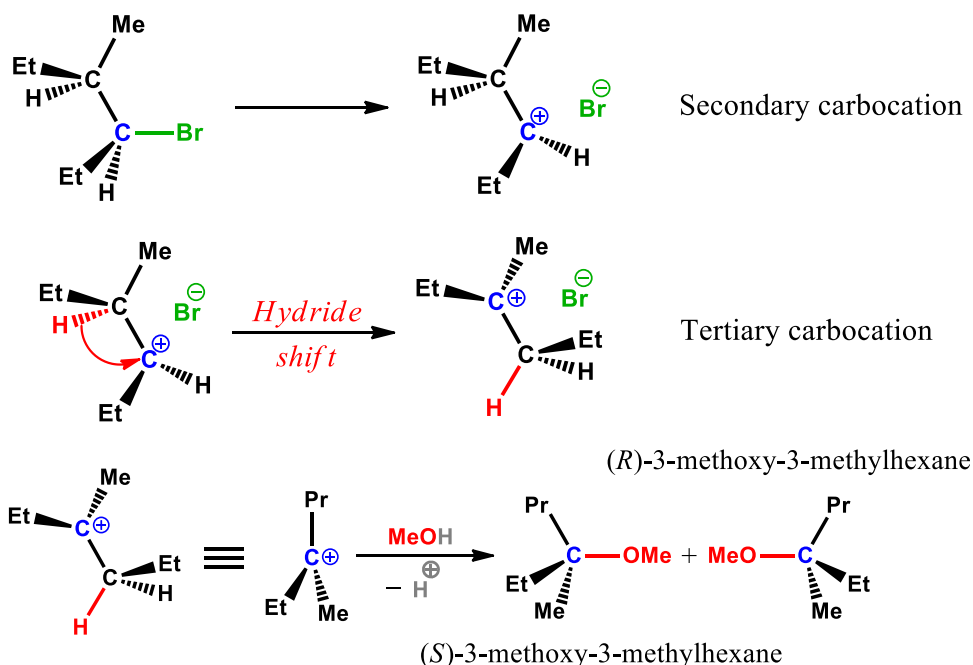
Hydride shift

Tertiary carbocation

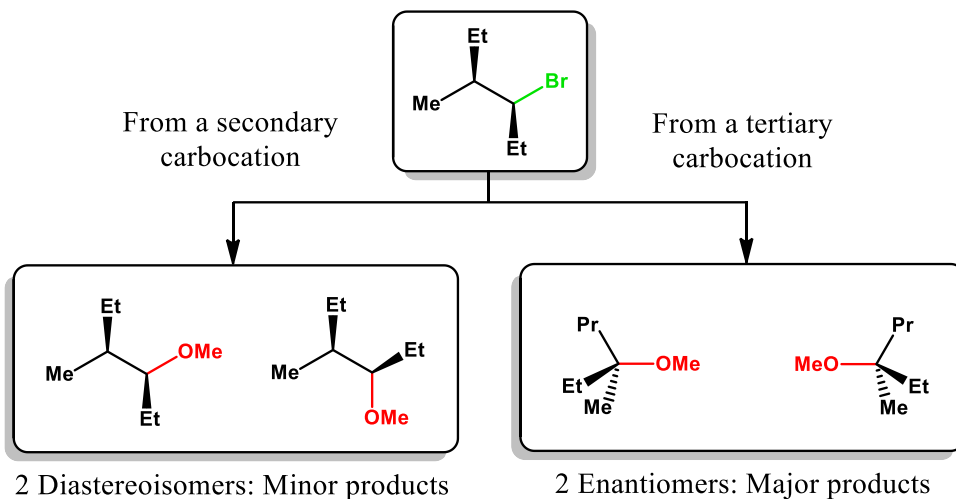
(*R*)-3-methoxy-3-methylhexane

MeOH

− H⊕

(*S*)-3-methoxy-3-methylhexane

Because of carbocation rearrangement, the reaction outcome would be four isomers. However, one stereoisomeric mixture would predominate over the other making this reaction a **regioselective reaction**.

2 Diastereoisomers: Minor products

2 Enantiomers: Major products

S_N1cA (Conjugate Acid) Mechanism

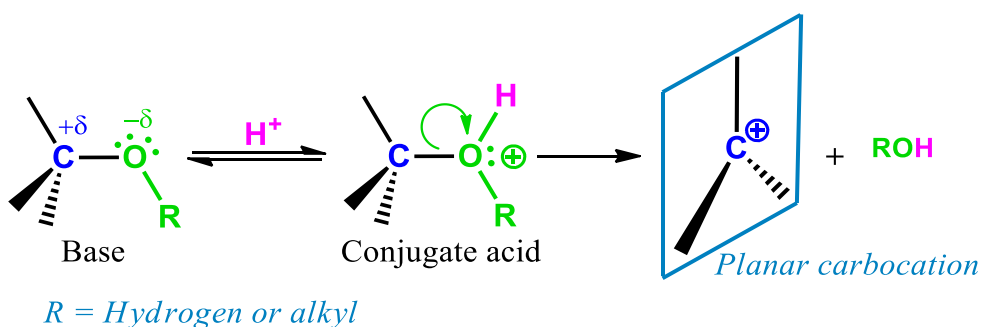
Unimolecular substitution can also proceed through an S_N1cA, mechanism also known as A1 mechanism, which differ from S_N1 only in the first step where an acid-base interaction occurs. This particular reaction occurs with alcohols and ethers "bases" where the oxygen gets protonated in order to form a better leaving group "conjugate acid".

+δ C —Ö: −δ R ⇌ H^+ C — O:⊕ H R → C⊕ + ROH

Base

Conjugate acid

Planar carbocation

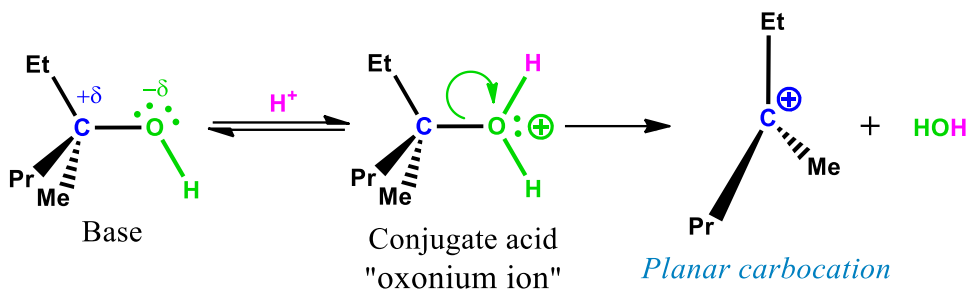
R = Hydrogen or alkyl

➲ ***Example***

A good example for S_N1cA reactions is reactions of a tertiary alcohol with hydrogen halide. In this case, the hydroxy group of the alcohol abstracts a hydrogen proton

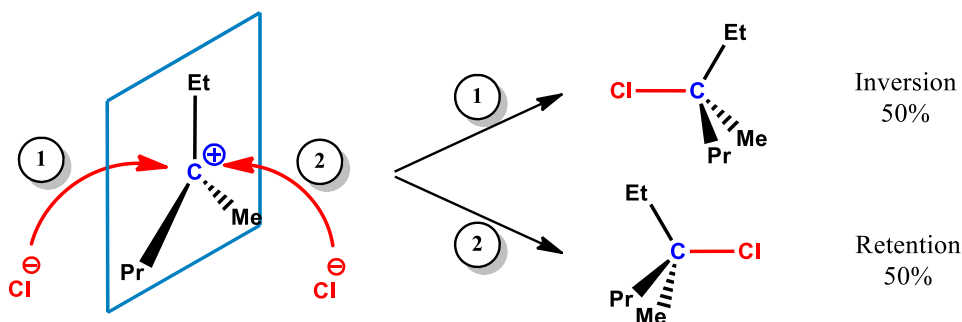
from the hydrogen halide moleculeto form an oxonium ion“conjugate base”. Once protonation is done, the leaving group “water” departs from the substrate creating, this way, a carbocation intermediate.

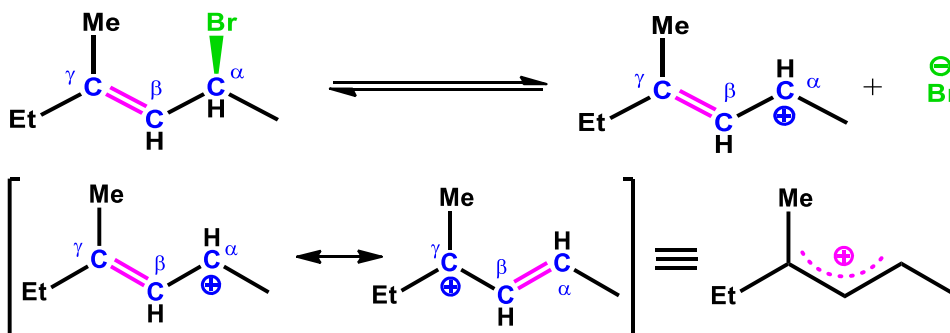
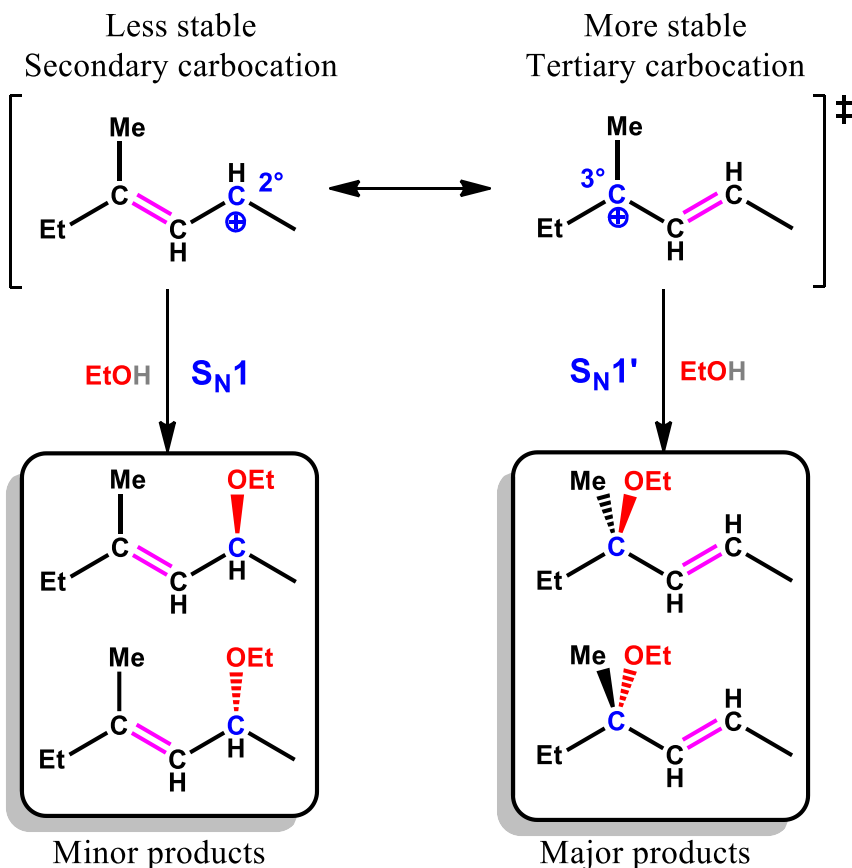
Base

Conjugate acid "oxonium ion"

Planar carbocation

Next, the reaction proceeds according to S_N1 mechanism where the nucleophilic halide attacks the carbocation from either sides.

Inversion 50%

Retention 50%

S_N1’ (Allylic Substitution) Mechanism

When the nucleofuge is attached to an allylic carbon atom, the substrate undergoes nucleophilic substitution reaction via an S_N1’ mechanism. In such a case, the carbocation intermediate formed is stabilized by resonance where the positive charge is distributed between the two carbons α and γ.

At this point, the nucleophile can attack α carbon via S_N1 mechanism or γ carbon via S_N1' mechanism. Reactions that involves S_N1' mechanism are **non-stereoselective** because both stereoisomers form. Nevertheless, they are **regioselective** since the nucleophile preferentially attacks the most substituted allylic carbocation.

Kinetics

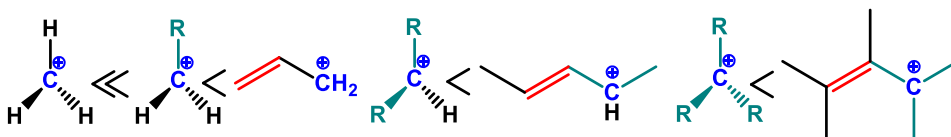
Unimolecular substitution reactions follow the first order kinetics where the reaction rate depends solely on the substrate concentration. As menti oned earlier, in unimolecular substitution reactions, nucleophiles do not intervene in the first step, which determine the overall rate of reaction. As a result, increasing or decreasing the concentration of the nucleophile will not change the velocity of reaction.

$$\text{Rate} = \text{K[Substrate]}$$

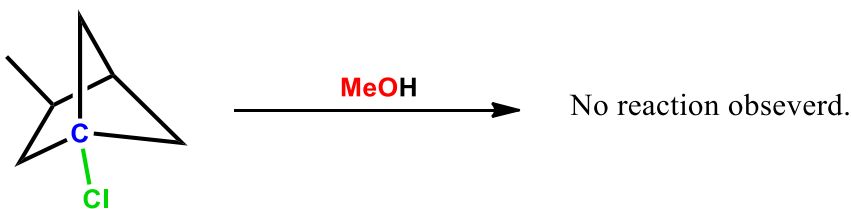
Reaction Conditions

Unimolecular substitution reactions are not possible unless certain conditions are met. These conditions includes substrate type, nucleophile strength, stability of the nucleofuge, and the solvent used.

Substrate

Since S_N1 reaction involves ionic intermediate, it is important that the carbocation intermediate be stable. As a result, S_N1 is more likely to occur when the stability of carbocation is optimized by ERGs, 1,2-shifts, and allylic rearrangement. Consequently, S_N1 reaction is more favorable with tertiary carbocation, can occur with secondary carbocation, but never with a primary carbocation or methylium compounds. *Primary allylic and benzylic carbocations are exception.*

Furthermore, S_N1 reaction is rarely observed with fused system substrates in which the leaving group is attached to the bridgehead carbon atom. The reason behind this is that the overall shape of the substrate prevents the targeted bridgehead atom from attaining the planar geometry as the leaving group gets expelled. Nonetheless, if one ring is sufficiently large to allow the bridgehead atom to attain a planar geometry, S_N1 reaction becomes possible.

MeOH

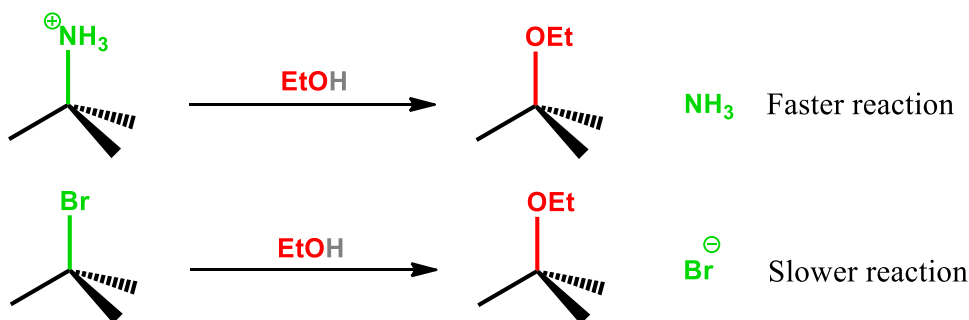
No reaction obseverd.

Leaving Group

In general, nucleophilic substitution reactions require a good leaving group that can be stable when it gets expelled from the substrate. However, the speed of S_N1 reaction is subjected to the stability of the leaving group. *The better a nucleofuge, the faster the reaction*. This is because the leaving group is involved in the rate-determining step. The illustration below shows some common nucleofuges arranged according to their stability in an ascending order.

$H_2N^- < HO^- < F^- << Cl^- < Br^- < H_2O \approx I^- < NH_3 < TsO^-$

In the example below, both reactions involve the same nucleophile, and both of them give the same product. However, the first reaction is faster than the second one because ammonia is a better leaving group than bromine.

$\overset{\oplus}{N}H_3$ —EtOH→ OEt NH_3 Faster reaction

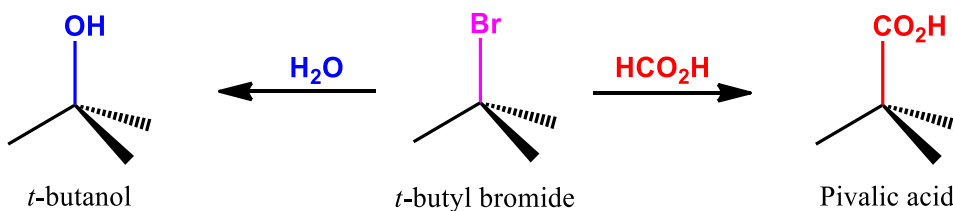
Br —EtOH→ OEt $Br^{\ominus}$ Slower reaction

Nucleophiles

In most cases, nucleophiles involved in S_N1 reaction are weak and neutral molecules such as MeOH, EtOH, and NH_3. Moreover, since nucleophiles are not involved in the rate-determining step, the strength of these nucleophiles is not important. Nevertheless, when more than one nucleophile are present in the reaction medium, they compete with each other. In such a case, the strength and the concentration of each nucleophile becomes significant and affect the distribution of products.

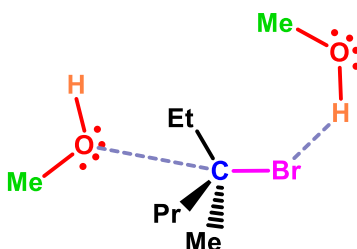
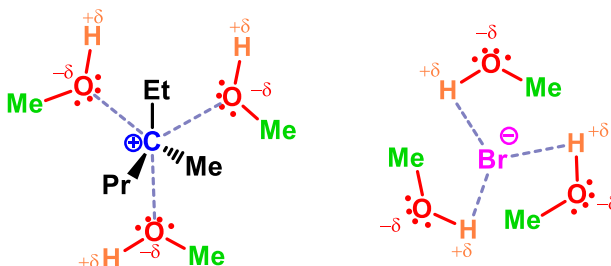
➲ ***Example***

If *t*-butyl bromide is treated with distilled water and formic acid, a mixture of two products would be obtained; *t*-butanol and pivalic acid where the yield of each product depends upon the concentrations and the nucleophilicity of HO^- and HCO_2^-.

OH ←H_2O— Br —HCO_2H→ CO_2H

t-butanol   *t*-butyl bromide   Pivalic acid

Solvent Effect

Polar protic solvents are efficient for S_N1 reaction; they facilitate the heterolysis of the nucleofuge and help stabilizing the carbocation intermediate. In contrast, polar aprotic solvents are not suitable for S_N1 reactions because they may react with the intermediate and thus lead to the formation of unwanted products.

In the first step, polar protic solvents form hydrogen bonds with the leaving group and therefore polarize the covalent bond that connects it to the substrate. This process facilitate the bond heterolysis.

After the leaving group get expelled, solvent molecules would surround it and form hydrogen bonds with it. Similarly, the carbocation formed would also get surrounded by the negative side of the solvent, which makes it more stable.

Bimolecular Nucleophilic Substitution Reactions S_N2

S_N2 Mechanism

S_N2 reactions are second order reactions that occur in one step only passing through a transition state to give a single product. At the transition state, the targeted carbon atom goes from sp^3 hybridization to sp^2 hybridization where the unhybridized p orbital is perpendicular on the trigonal plane. The nucleophile approaches the substrate and overlaps with one lobe of the unhybridized p orbital, which is on the opposite side of the leaving group. At this point, a new bond starts forming between the nucleophile and the substrate while the bond connecting the nucleofuge to the substrate breaks.

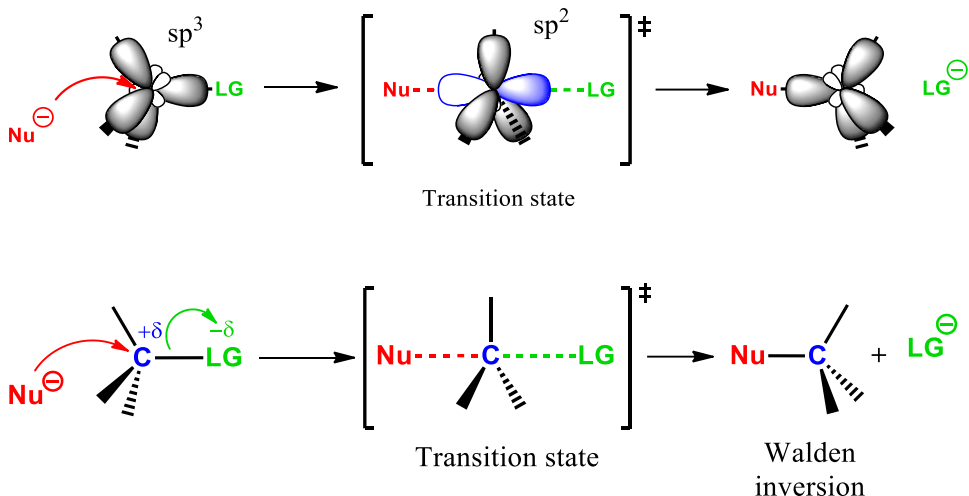
sp3 sp2 ‡

Nu⊖ LG Nu- - LG Nu LG⊖

Transition state

Nu⊖ +δ C LG −δ [Nu- - - - -C- - - - - -LG]‡ Nu—C + LG⊖

Transition state

Walden inversion

S_N2 reaction is a **regiospecific** reaction whereby the nucleophile attacks the targeted carbon atom exclusively from the opposite side of the leaving group "*anti*-attack". As a result, the stereochemistry of the final product depends upon the stereochemistry of the substrate, which makes S_N2 reaction **stereospecific** that gives the inversion product.

➲ ***Example:***

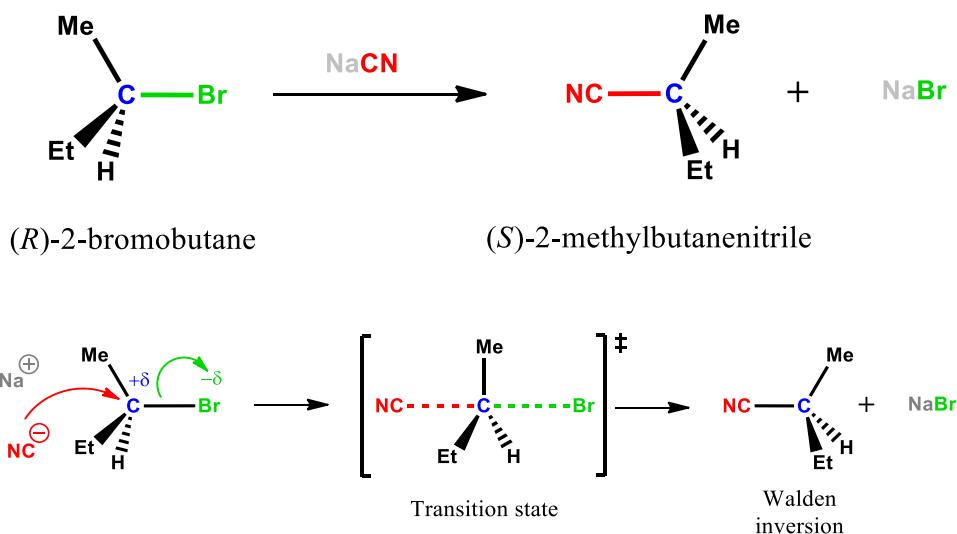
Reaction of (*R*)-2-bromobutane with aqueous sodium cyanide gives (*S*)-2-methylbutanenitrile.

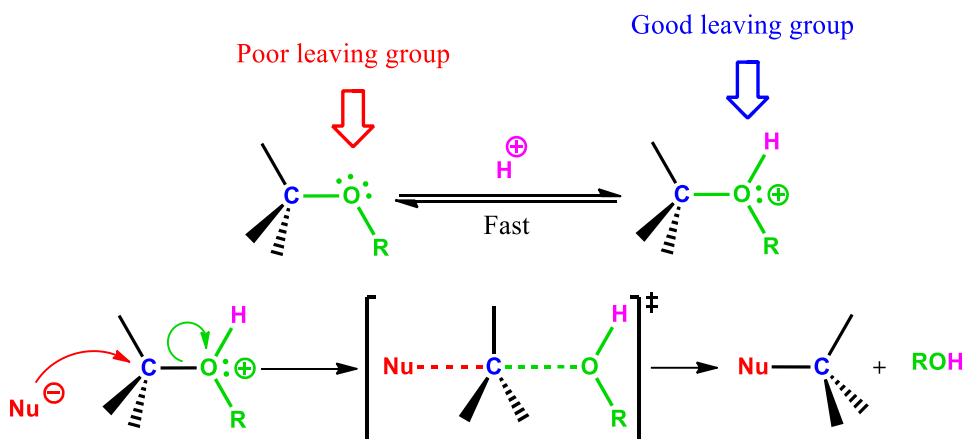
Me, C—Br, Et, H —NaCN→ NC—C, Me, H, Et + NaBr

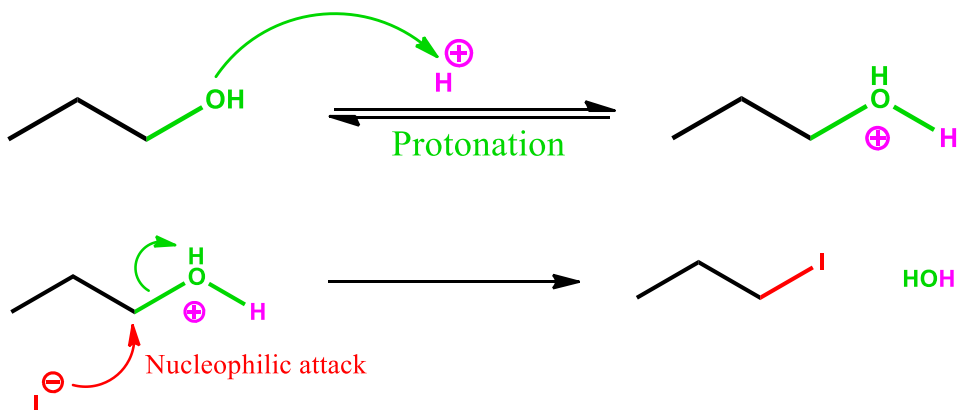
(*R*)-2-bromobutane (*S*)-2-methylbutanenitrile

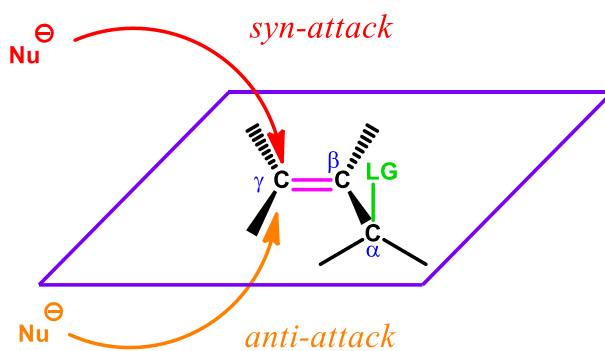
Na⊕ NC⊖ Me +δ C Br −δ Et H → [NC- - - - -C- - - - - -Br (Me, Et, H)]‡ → NC—C (Me, H, Et) + NaBr

Transition state

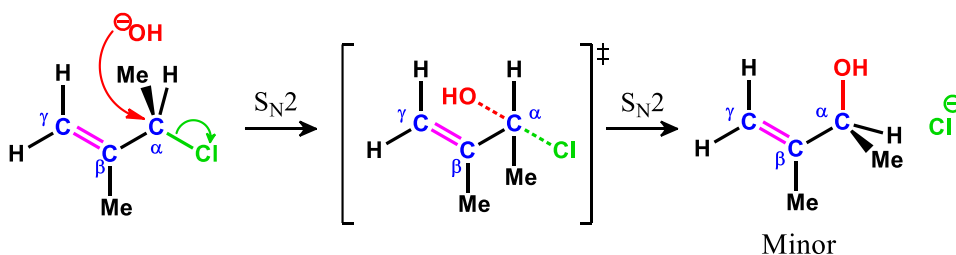
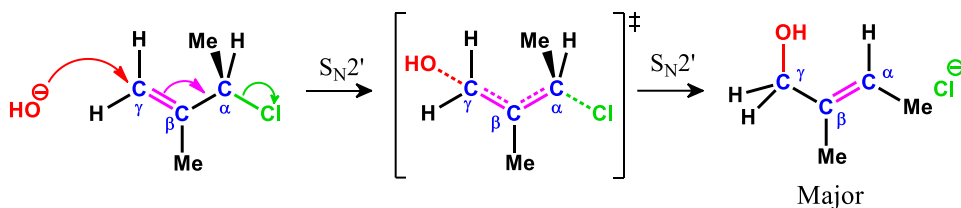
Walden inversion

S_N2cA (Conjugate acid) Mechanism

Before undergoing a bimolecular substitution reaction, certain substrates require an additional step that consists in converting the leaving group into a better nucleofuge. In this case, the overall reaction is known as S_N2cA reaction, which involves acid-base interaction whereby the leaving group gets protonated (conjugate acid). This reaction is common with alcohols and ethers.

➲ ***Example:***

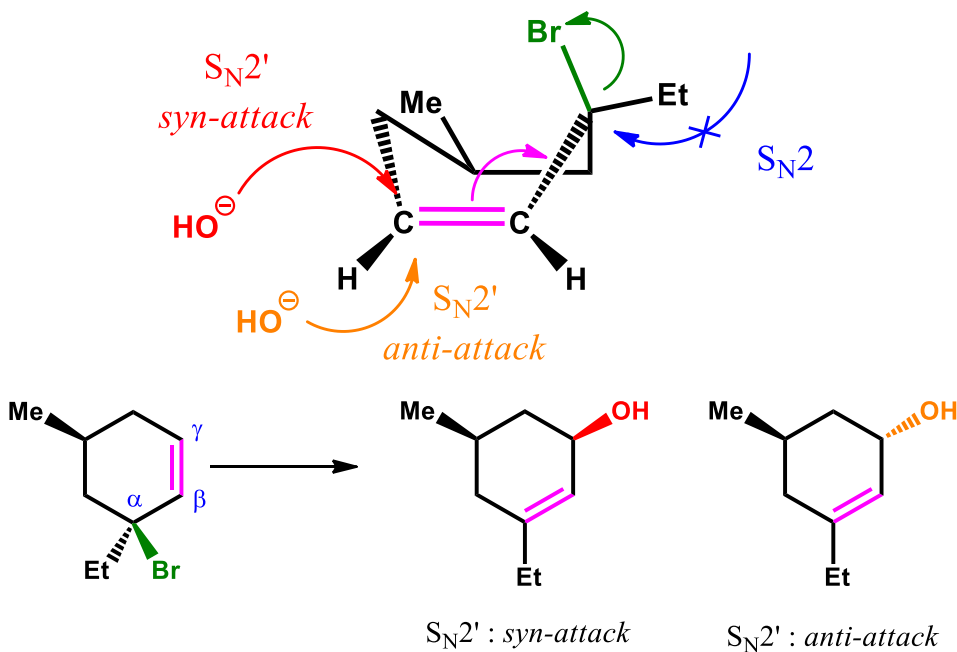
Primary alcohols react with strong hydrogen halides such as HBr and HI to give the corresponding alkyl halide and a water molecule. In such reaction, the hydroxy group cannot be displaced by the nucleophilic halide unless it is protonated. For that, before nucleophilic attacks takes place, the hydroxy group must gets protonated to generate a better leaving group. At this point, the nucleophile attacks the targeted carbon atom from the backside, which leads to the formation of alkyl iodide and a water molecule.

S_N2' (Allylic Substitution) Mechanism

Allylic and benzylic compounds can also undergo S_N2 reaction when reaction conditions are met. In such a case, the nucleophile may attack α carbon via S_N2 mechanism or γ carbon via S_N2' mechanism depending upon the steric hindrance of each carbon atom. Allylic compound with a primary or secondary α carbon favor S_N2 reaction. However, tertiary α carbons or secondary α carbon with bulky alkyl group disfavor S_N2 reaction. In this case, the reaction proceeds exclusively via S_N2' mechanism. Furthermore, the size of the nucleophile also plays an important role in determining which mechanism is more favorable. In addition, in case of S_N2' mechanism, the nucleophile can attack from either sides of the π bond. If the nucleophile attacks the γ carbon from the same side of the leaving group, the attack is referred to as *syn-attack*. On the other hand, when nucleophilic attack occurs on the opposite side of the leaving group, then it is called *anti-attack*.

Example 1

In this example, α carbon is secondary whereas γ is primary. In this case, the nucleophile can attack both of them because although α carbon is secondary, it is not sterically hindered enough to impede the nucleophilic attack. Besides, the nucleophile used is not bulky. However, there would be more S_N2' products than S_N2 products, which makes reactions that involve S_N2' mechanism **regioselective** since the nucleophile preferentially attacks the least hindered carbon atom.

Minor

➲ ***Example 2***

In this example, α carbon is tertiary whereas γ carbon is secondary. As a result, the reaction would exclusively proceed via S_N2' mechanism.

S_N2' : *syn-attack* S_N2' : *anti-attack*

Because the nucleophilic attack can occur via *syn* or *anti* attacks, S_N2'reaction is **non-stereoselective**.

Kinetics

Bimolecular nucleophilic substitutions follow the second order kinetics. Their rates depend upon the concentration of both reagents; the nucleophile and the substrate. This is because both of them are involved in the rate-determining step.

$$\text{Rate} = \text{K[Substrate][Nucleophile]}$$

Although this equation was found to accurate for many reactions in organic chemistry, experiments showed that when undergoing reactions that involve excess

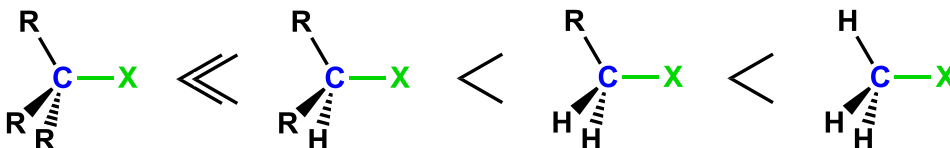
of nucleophile, the rate will be first order instead of second order. In this case, the rate of the reaction would depend solely on the concentration of the substrate. These reactions are referred as pseudo first order.

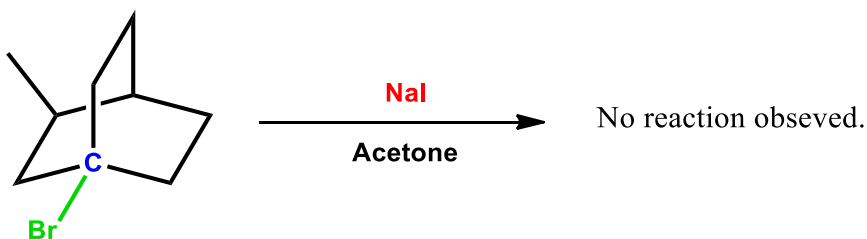
$$\text{Rate} = K[\text{Substrate}]$$

Reaction Conditions

The following conditions determine whether a S_N2 reaction is possible or not.

Substrate

S_N2 reaction depends upon the steric hindrance of the targeted carbon atom. the more sterically hindered the substrate, the less reactive. As a result, S_N2 reaction is more favorable with methylium compounds “methyl halides, primary alcohols” and primary substrates. For secondary substrates, on the other hand, S_N1 and elimination reactions compete with S_N2 reaction where a mixture of product may be produced. In case of tertiary alkyl compounds, S_N2 reaction is not observed.

Moreover, when the leaving group is attached to a bridgehead carbon of a polycyclic, S_N2 reaction cannot take place due to the steric hindrance that prevents the nucleophile from approaching the targeted bridgehead carbon atom.

NaI
Acetone
No reaction obseved.

Leaving Group

Just like S_N1 reaction, S_N2 reaction also requires a good leaving group that forms a stable ion when it gets expelled from the substrate.

Nucleophile

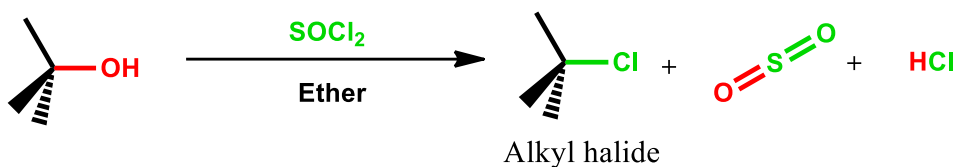
In S_N2 reaction, the concentration, strength, and size of the nucleophile are important. As the concentration of the nucleophile increases, the reaction proceeds faster. Furthermore, S_N2 reaction requires strong nucleophiles “generally anionic” in order to avoid the formation of a carbocation intermediate and therefore turn into an S_N1 reaction. In addition, the nucleophile has to be small enough to be able to attack the targeted carbon atom.

Solvent

Polar protic solvents slow down S_N2 reactions as they capture the strong nucleophile forming hydrogen bonds with it. However, using a polar aprotic solvent improves nucleophile nucleophilicity and help polarizing the bond attaching the nucleofuge to the substrate.

Internal Nucleophilic Substitution S_Ni

Internal nucleophilic substitution reaction is relatively rare reaction that follows first order kinetic. In contrast to S_N2 reaction that leads to the inversion of configuration, S_Ni reaction gives the retention product. This reaction con sists in converting a substrate “alcohol” to an alkyl halide.

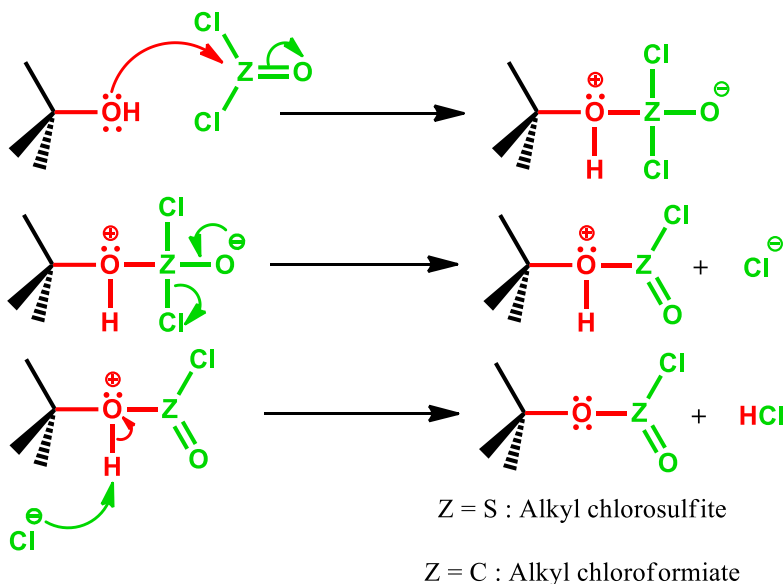
SOCl2
Ether
HCl
Alkyl halide

Mechanism

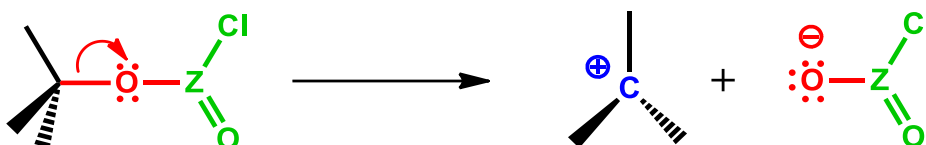
S_Ni reaction is carried out with thionyl chloride $SOCl_2$ or phosgene $COCl_2$ in the presence on an ether and it proceeds in two steps after the preparation step.

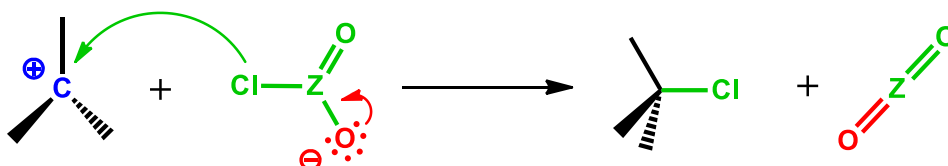
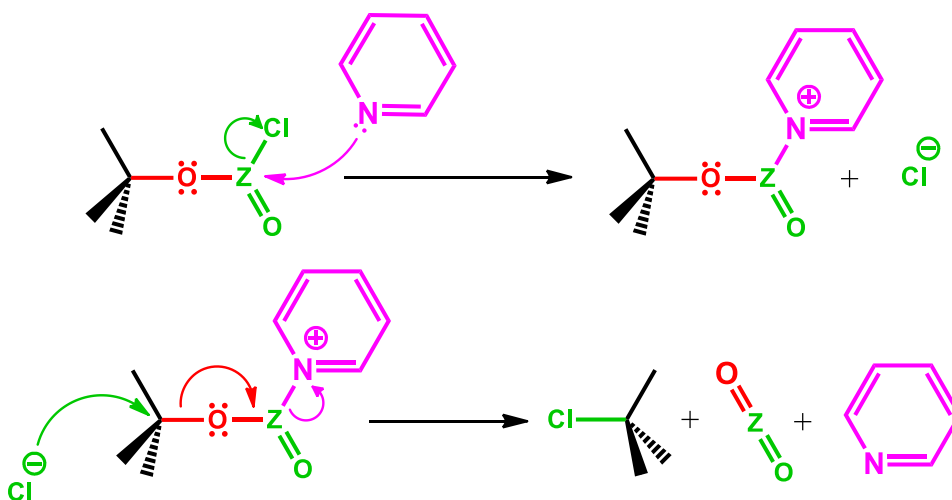
Preparation step

This step consists in converting the substrate into an alkyl chlorosulfite or an alkyl chloroformiate. At this point , an S_N2 reaction takes place whereby the hydroxy group of the substrate attacks either thionyl chloride or phosgene in order to create a better leaving group.

Z = S : Alkyl chlorosulfite

Z = C : Alkyl chloroformiate

Step one

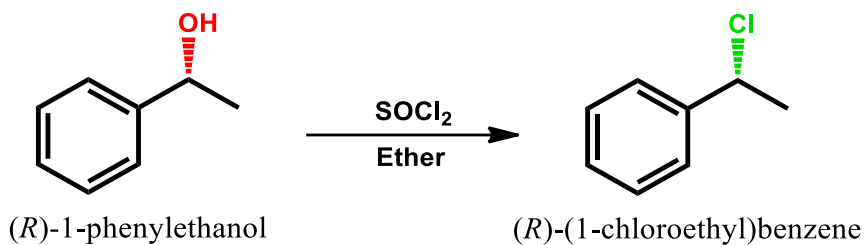
The first step is similar to S_N1 reaction. At this point, the bond between the substrate and the leaving group get polarized and then the nucleofuge get expelled resulting in a carbocation intermediate.

Step two

In the second step, the nucleofuge expelled would act as a nucleophile and attack the carbocation from the same side the nucleofuge got expelled forming, as a result, the product with retention of configuration.

In case of performing the reaction under a basic condition, S_N2 reaction would take place instead of S_Ni reaction. In this case, the base would react with the substrate "alkyl chlorosulfite or alkyl chloroformiate" at first to form an organic salt. Then, the chloride ion would attack the targeted carbon from the opposite side to the leaving group resulting in inversion of configuration.

➲ *Example*

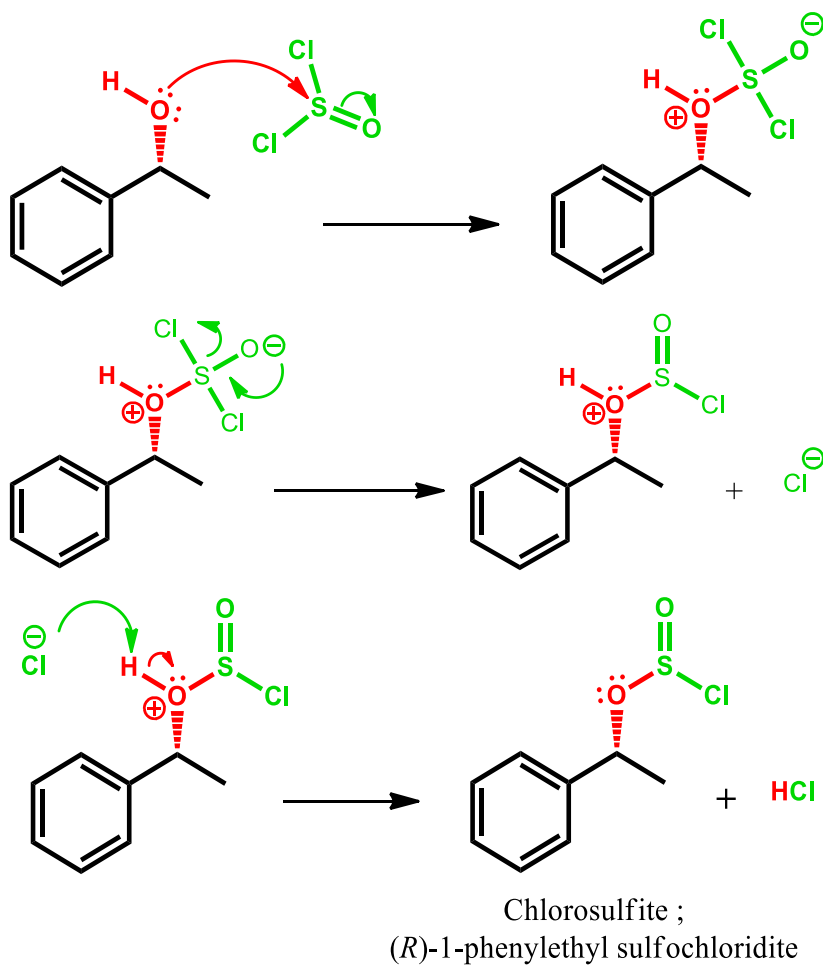
Reaction of (*R*)-1-phenyl ethanol with thionyl chloride in ether.

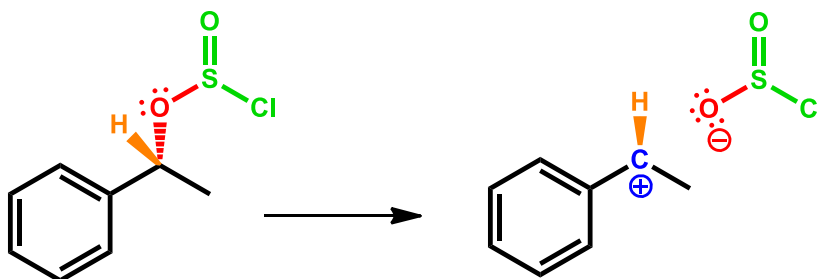
$SOCl_2$

Ether

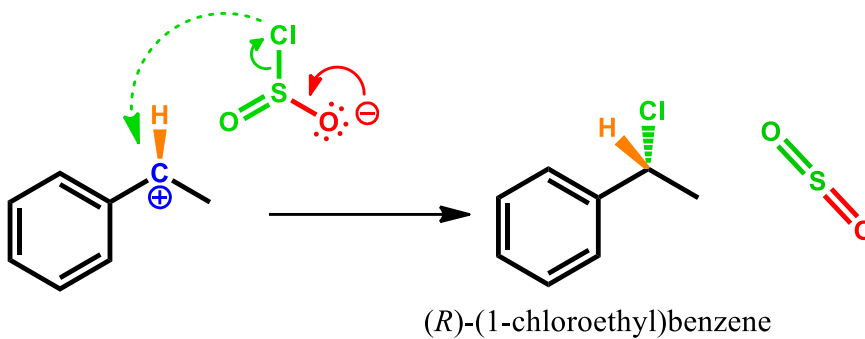
(*R*)-1-phenylethanol (*R*)-(1-chloroethyl)benzene

Preparation step

This step consists in forming the corresponding chlorosulfite from (*R*)-1-phenyl ethanol.

Chlorosulfite ;
(*R*)-1-phenylethyl sulfochloridite

First step

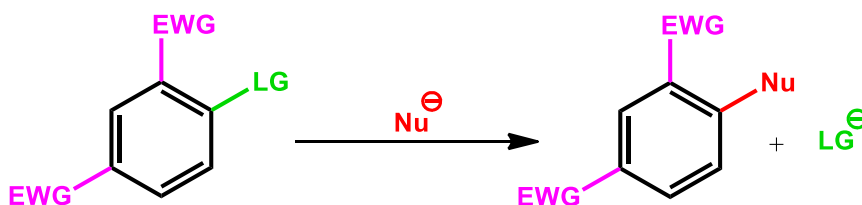
After the chlorosulfite is formed, the leaving group dissociates resulting in a carbocation intermediate and sulfochloridite.

Second step

The final step is characterized by the nucleophilic attack of the chlorineattached to the sulfochloridite on the carbocation from the same side the nucleofuge has left, which gives (*R*)-(1-chloroethyl)benzene.

(*R*)-(1-chloroethyl)benzene

III. 1. 2. 2. Nucleophilic Aromatic Substitution Reactions

Aromatic compounds are so stable that nucleophilic substitution reactions are impossible when the targeted carbon atoms belongs to the aromatic system. Nevertheless, some aromatic compounds that have specific structuralproperties do undergo nucleophilic substitution reactions such as S_NAR, S_N1, and $S_{RN}1$.

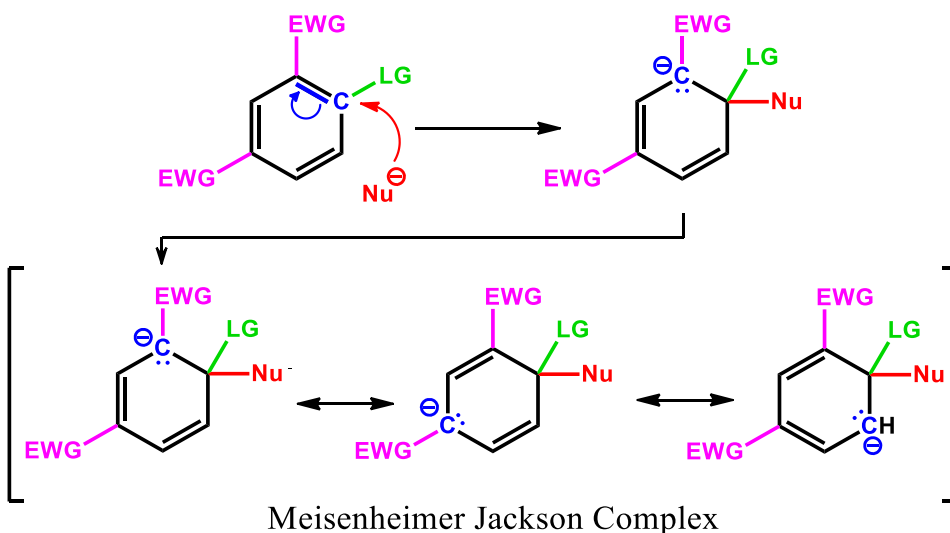
S_NAr Reaction

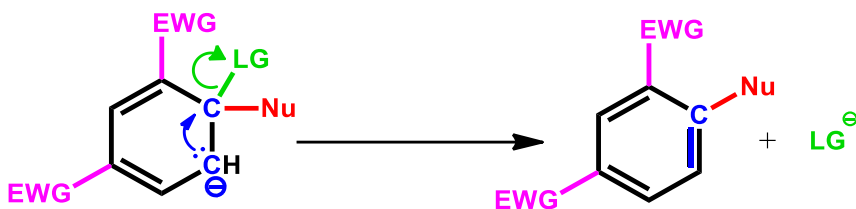
S_NAr reaction is specific for aromatic compounds that contain electron-withdrawing groups EWGs, mainly on *ortho* and *para* positions with respect to the leaving group, which help in minimizing electron density ofthe targeted sp^2 carbon of the aromatic ring.

Mechanism

S_NAr reaction is the most common aromatic nucleophilic substitution reaction and it proceeds in two steps.

Step one

The first step is a slow process in which the nucleophile adds to the carbon atom attached to the leaving group. At this point, an anionic intermediate forms known as ***Meisenheimer Jackson complex***. This particular intermediate can be isolated from the reaction medium due to its stability, which is maintained by the electron withdrawing effect of the EWG on *ortho* and/or *para* positions.

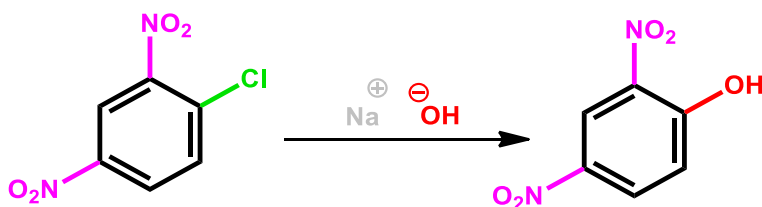
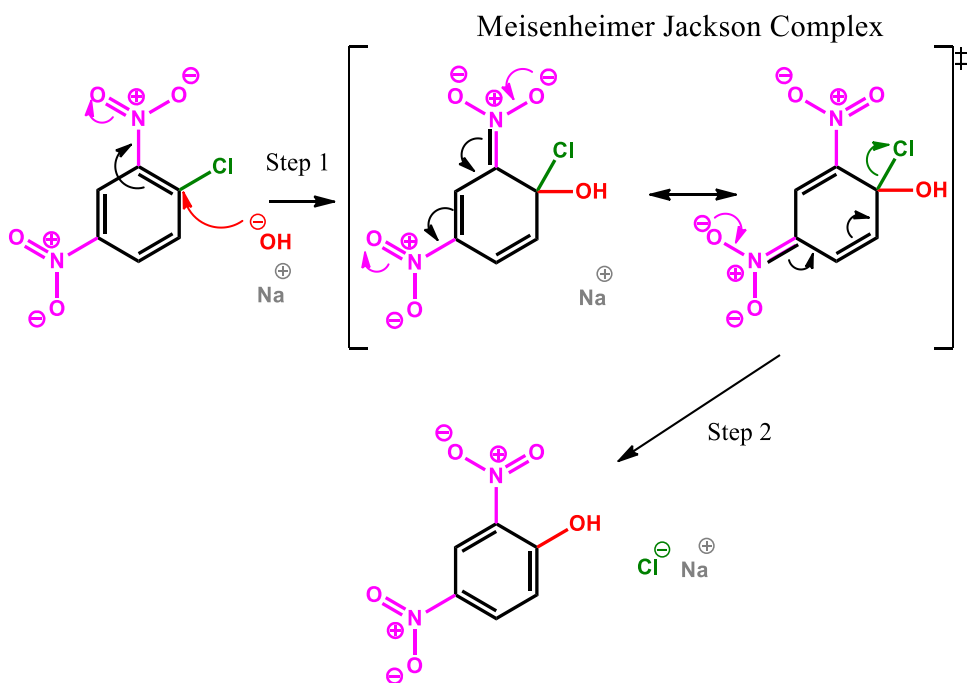
Meisenheimer Jackson Complex

Step two

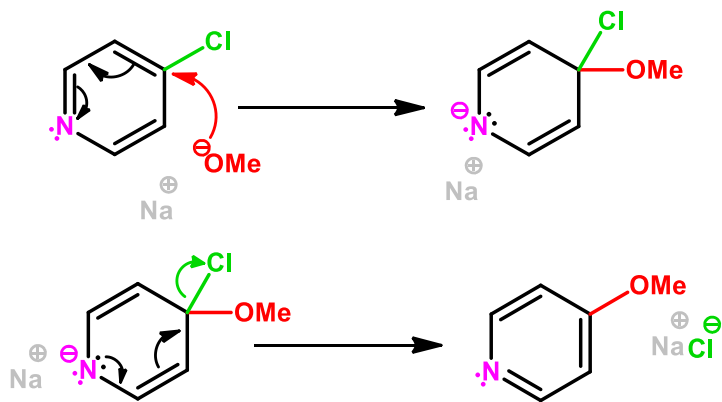
The second step is a fast process where the leaving group gets removed from the substrate, which leads to the restoration of the compound aromaticity.

Furthermore, it is important to know that EWG s are activating groups that favor S_NAr reaction especially when they are in positions *ortho* and/or *para*. In contrast, electron releasing groups ERGs disfavor S_NAr reaction.

➲ ***Example 1***

Meisenheimer Jackson Complex

Step 1

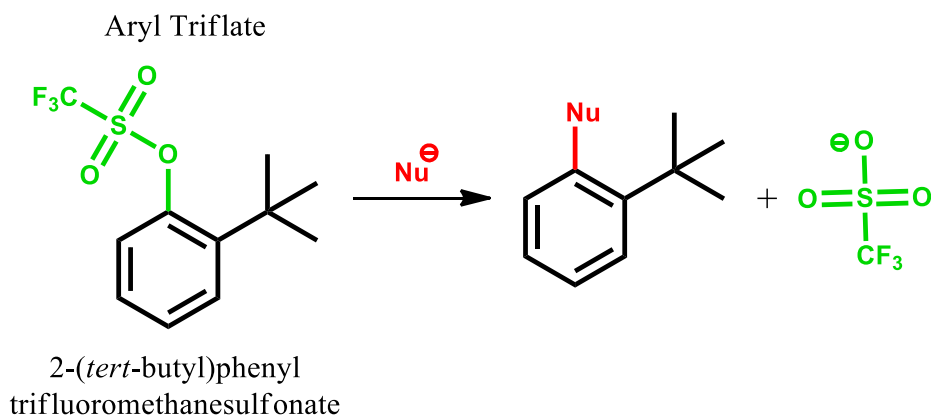
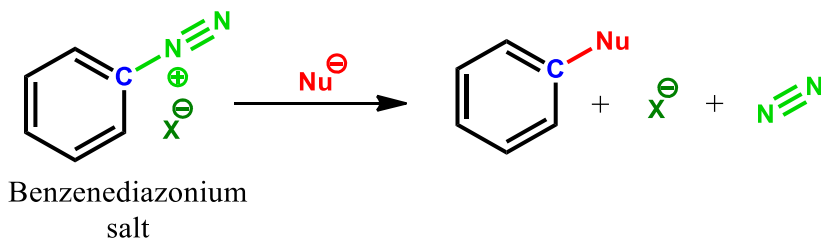
Step 2

➲ *Example 2*

S_NAr reaction is also possible and largely used with pyridine compounds.

S_N1 Aromatic Reaction

S_N1 reaction is exclusive for benzenediazonium salts and their derivatives, and exceptional for aryl triflate compounds that contain a bulky substituent on ortho position.

Benzenediazonium salt

Aryl Triflate

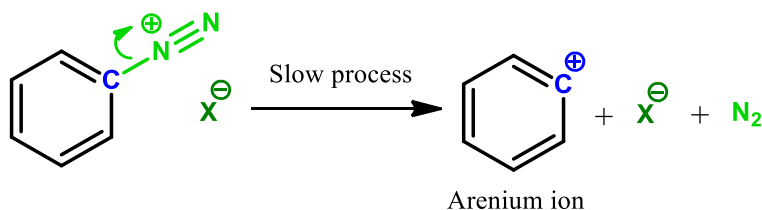
2-(*tert*-butyl)phenyl trifluoromethanesulfonate

Mechanism

Just like aliphatic S_N1 reaction, aromatic S_N1 reaction is a first order reaction that proceeds in two steps.

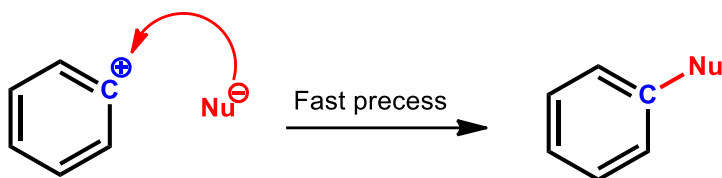
Step one

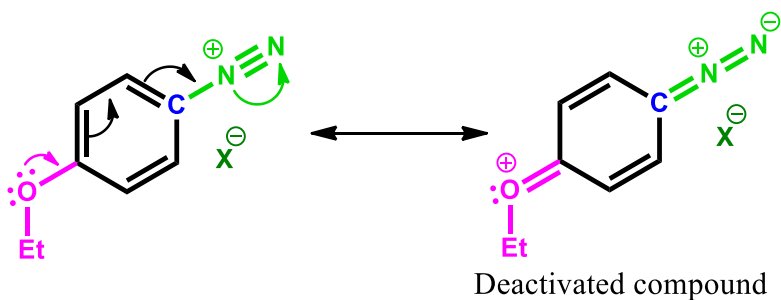
The first step is a slow process where a carbocation forms as the leaving group gets expelled from the substrate as dinitrogen molecule N_2. This particular carbocation is so reactive and it is referred to as arenium ion.

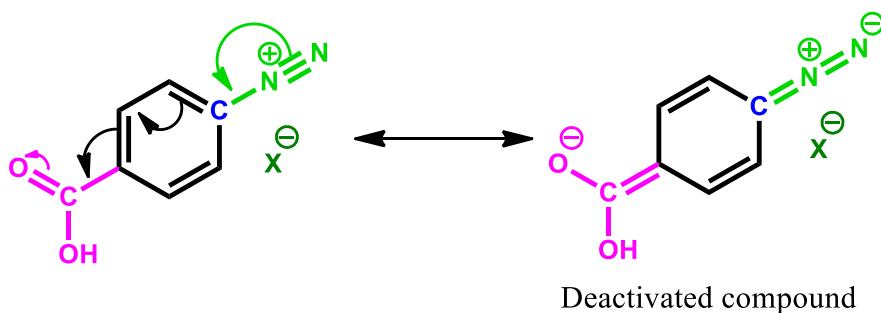
Slow process

Arenium ion

Step two

The next step is a fast process where the nucleophile attacks the carbocation forming a new covalent bond with it.

Fast precess

Furthermore, it is important to know that electron releasing groups ERG on para position disfavor S_N1 aromatic reaction for they stabilize the benzenediazonium ion through donor mesomeric effect +*M*.

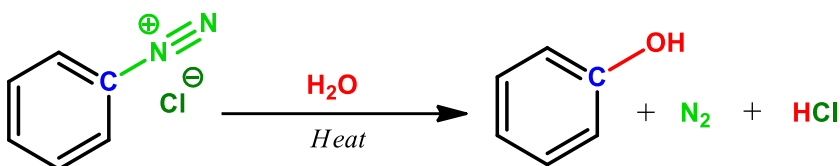
Deactivated compound

Similarly, electron withdrawing groups EWG on para position also disfavor S_N1 aromatic reaction due to the –*M* effect that stabilize the benzodiazonium ion.

Deactivated compound

➲ ***Example***

Preparation of phenol from benzenediazonium chloride is accomplished by treating the benzenediazonium chloride with water in a warm condition.

H_2O

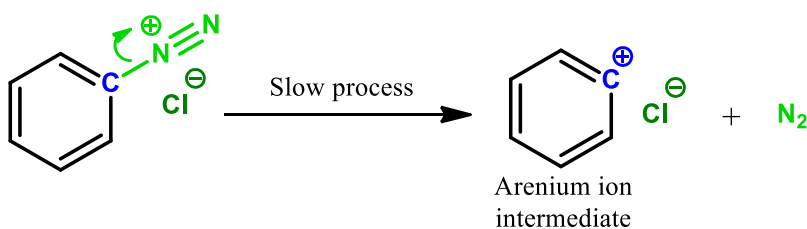
Heat

$+ N_2 + HCl$

Step one

Because diazo group is a good leaving group, heating an aqueous solution of benzenediazonium chloride will drive the diazo group to leave the substrate as nitrogen gas resulting in an arenium ion intermediate.

Slow process

$+ N_2$

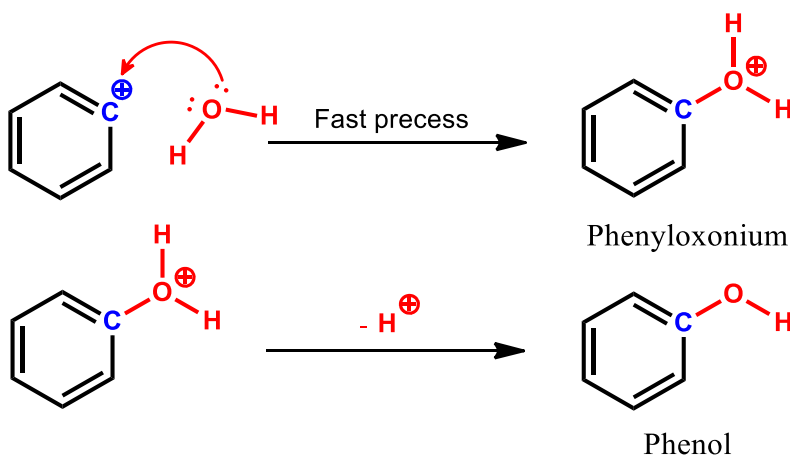
Arenium ion intermediate

Step two

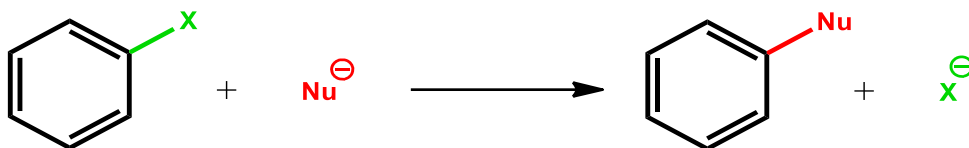
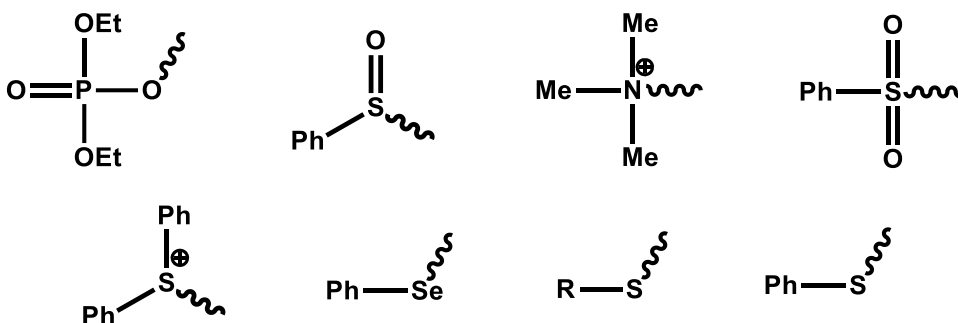
In the next step, water molecule would capture the carbocation and forms phenyloxonium ion, which then gets deprotonated to give phenol.

Fast precess

Phenyloxonium

$- H^{\oplus}$

Phenol

$S_{RN}1$ Reaction

$S_{RN}1$ reaction stands for unimolecular radical-nucleophilic substitution reaction. It is a chain reaction that consists in replacing a leaving group by a nucleophile through intermediary free radical species.

$S_{RN}1$ reaction is suitable for benzene, benzene derivatives, polycyclic aromatic compounds, and heteroaromatic compounds that contain a leaving group. In most case, this leaving group is a halogen atom, however, many other leaving groups –*listed below*– have been found to be compatible for $S_{RN}1$ reaction.

Furthermore, $S_{RN}1$ reactions involve carbanion nucleophiles that have a general formula $R-\overset{\ominus}{C}H-Z$ where R is an alkyl or phenyl group while Z is CN, C(O)R', C(O)OR', or C(O)N(R')(R'').

Mechanism

$S_{RN}1$ reaction mechanism proceeds in three step, initiation, propagation, and finally termination.

Initiation

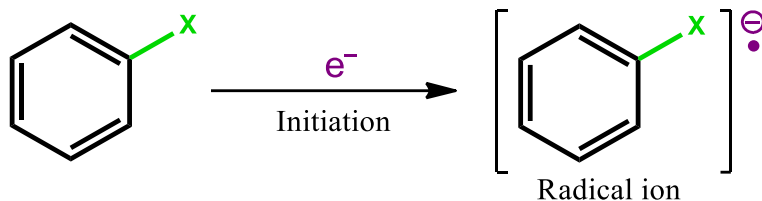
The first step is characterized by a single electron transfer **SET** in which the substrate accept one electron from an electron donor species resulting in a radical ion intermediate. This process can be accomplished by several methods such as photostimulation, solvated e1ectrons, or by electrochemical method.

X

e⁻

Initiation

X

Radical ion

Propagation

In this step, the radical anion collapses into an aryl radical and a halide anion.Later on, the nucleophile would react with the aryl radical resulting in a new radical anion.

X

Radical ion

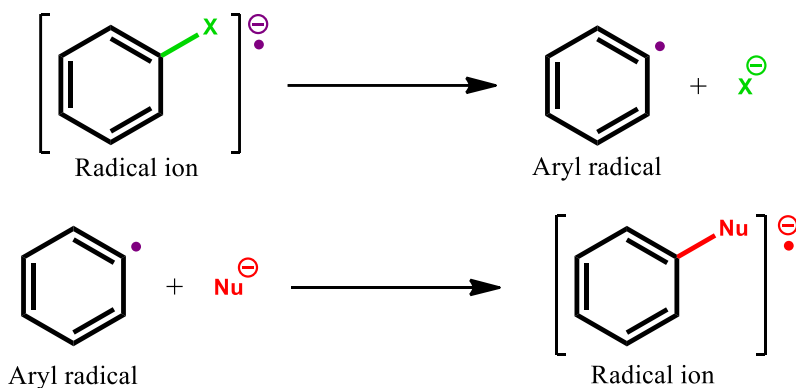
Aryl radical

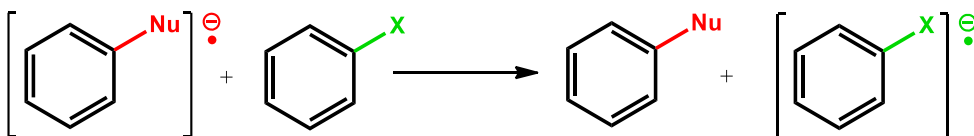
+ X

Aryl radical

+ Nu

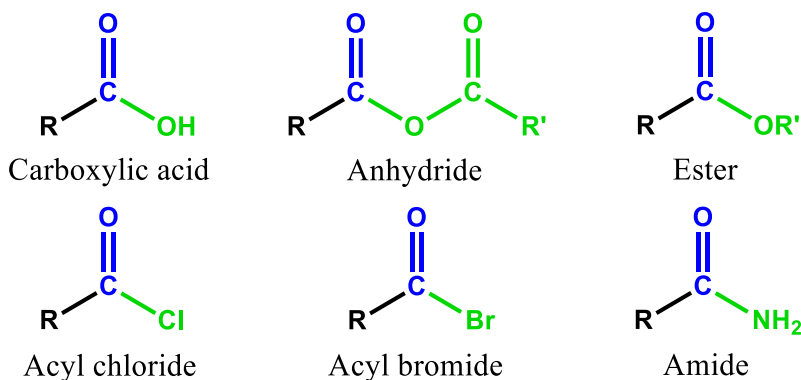
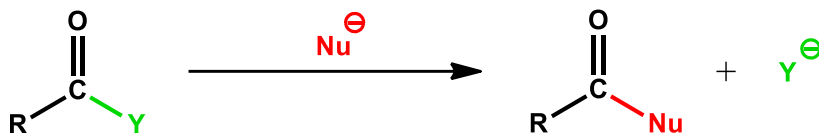
Nu

Radical ion

Later on, this radical anion, which bears the nucleophile would react with another aryl halide to form a new radical anion along with the final aromatic product.

Nu + X → Nu + X

Termination

Finally, the reaction stops when there no more reagent are left to react. This step may depend upon several factors including the type initiation, the intermediates involved, and solvent used and it is not thoroughly understood yet.

III. 1. 2. 3. Nucleophilic Substitution of Carboxylic acids and their Derivatives

Carboxylic acids are organic compounds that possess a carboxy group –C(O)OH. This particular functional group consists of a carbonyl attached to a hydroxy group. Carboxylic acid derivatives are modified carboxylic acids where the hydroxy group is replaced by another substituent. These compounds are represented by the general formula "RC(O)Y" where Y is a halogen for acyl halides, –OC(O)R' for anhydrides, –OR for esters, or $-NR_2$ for amides. Moreover, all carboxylic acid derivatives can be converted into their corresponding carboxylic acid by hydrolysis.

Carboxylic acids and their derivatives undergo nucleophilic substitution reaction whereby the leaving group –Y gets displaced upon nucleophilic attack on the carbonyl carbon.

Mechanism

Nucleophilic substitution reactions of carboxylic acids and their derivatives proceed in two steps; addition of the nucleophile to the carbonyl carbon followed by elimination of the leaving group. This reactionmay or may not require a catalyst depending upon the nature of the leaving group and the nucleophile involved.

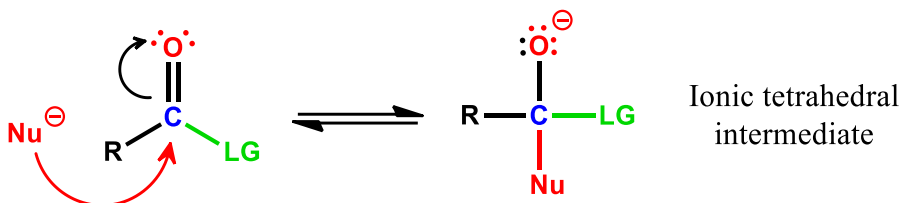
Non-catalyzed Reactions

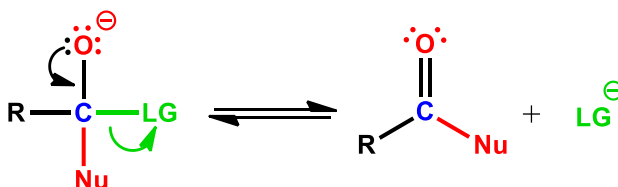
In case of using a strong anionic nucleophile such as a hydroxide or an alkoxide, the use of catalyst may not be necessary since the nucleophile is strong enough to attack the electrophilic site "carbonyl carbon". Moreover, when the substrate

contains a good leaving group such as acyl halides or esters, even when using a weak nucleophile the reaction does not require a catalyst.

Step one

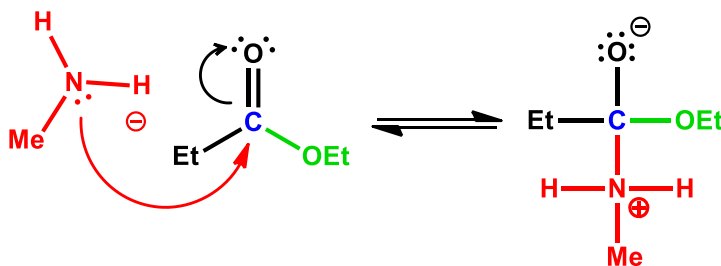
The first step is characterized by nucleophilic addition to the carbonyl carbon and the formation of an ionic tetrahedral intermediate.

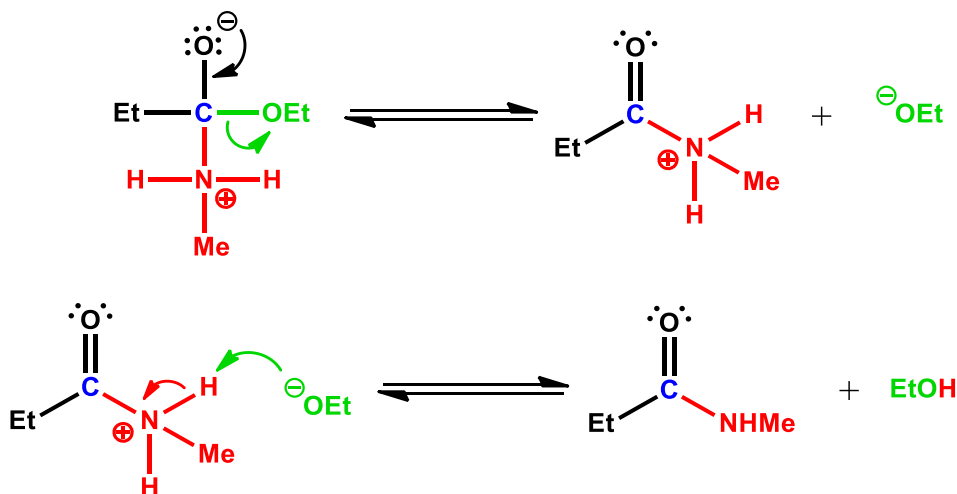
Ionic tetrahedral intermediate

Step two

The next step consists in reforming the carbonyl functional gro up and the elimination of the leaving group.

➲ *Example*

Reaction of esters with amines leads to the formation ofthe corresponding amides. In this case, although the amine is a weak nucleophile, it is su fficiently strong to react with ester because the leaving group alkoxide RO $^-$ can easily be removed from the carbonyl (good leaving group).

Step one

Addition of amine to the carbonyl and the formation of tetrahedral ionic intermediate.

Step two

Elimination of ethoxide followed by deprotonation of amines.

Catalyzed Reaction

When a weak non-ionic nucleophile such as water, ethanol, or amines is used, the reaction must be promoted by acid or base catalysis.

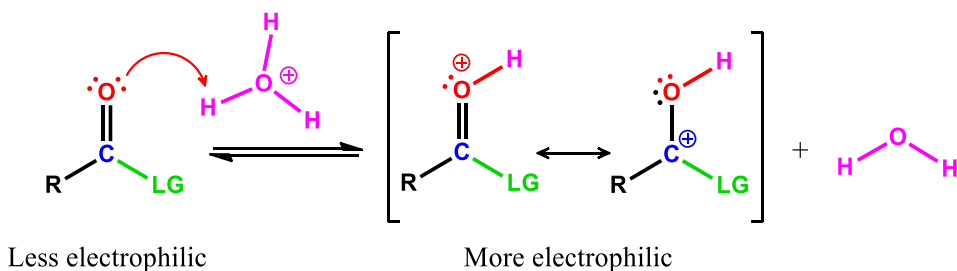
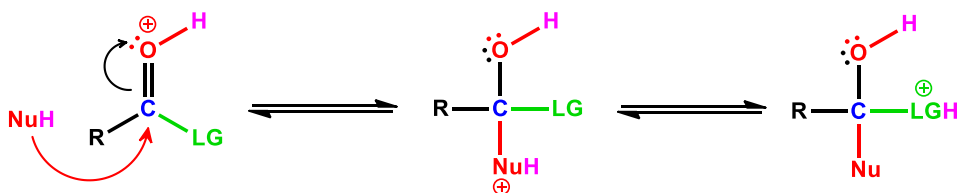
Acid catalyzed reactions

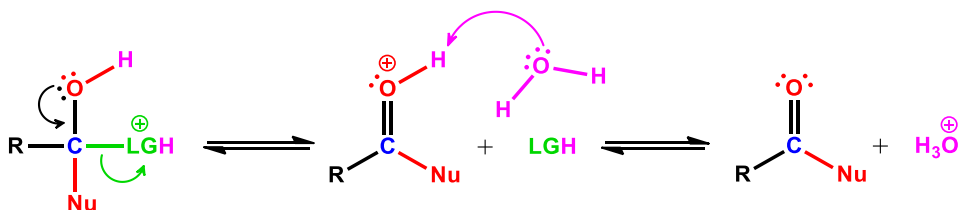
Acid catalyzed reactions consist in increasing the electrophilicity of the carbonyl carbon by protonating the oxygen atom of the carbonyl.

Step one

The first step consists in protonating the carbonyl oxygen, which makes the carbonyl carbon more electrophilic. At this point, nucleophilic attack can readily take place leading to the formation of a tetrahedral intermediate.

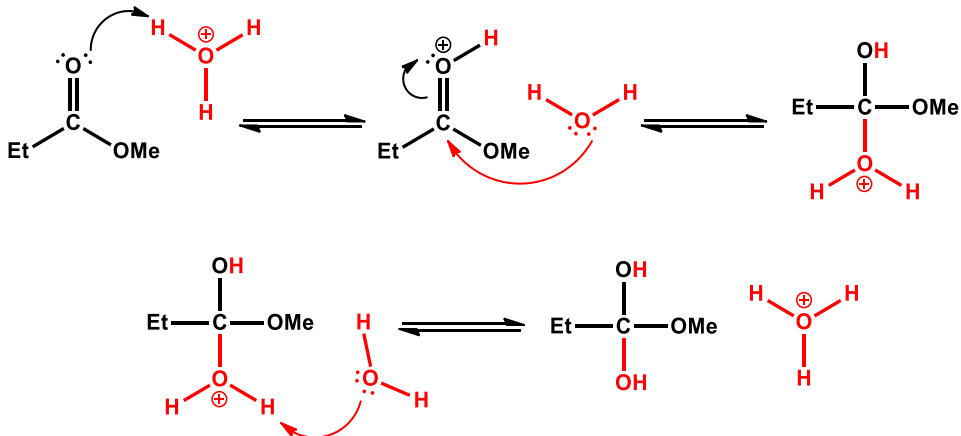
Less electrophilic

More electrophilic

Step two

The next step consists in reforming of the carbonyl functional group and eliminating the leaving group. This process leads to a protonated carbonyl, which then gets deprotonated by a nearby basic species"water molecule or conjugate base of the acid catalyst".

➲ ***Example***

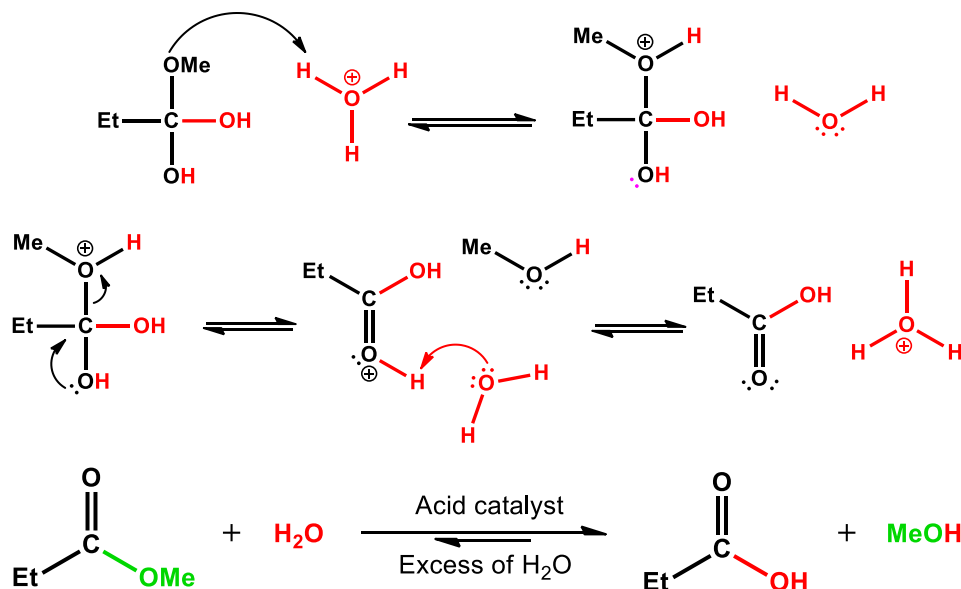
Acid catalyzed hydrolysis of esters gives the corresponding carboxylic acid.

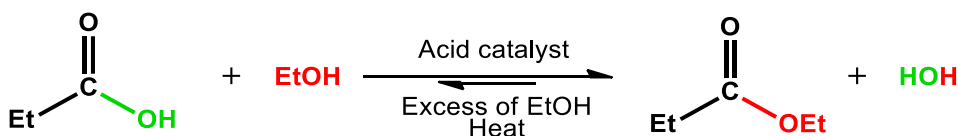
Step one

Initially, the carbonyl oxygen gets protonated in order to optimize carbonyl carbon electrophilicity. Later on, a water molecule will add to the carbonyl carbon resulting in a tetrahedral diol. This step is reversible.

Step two

The next step is also a reversible where the leaving group gets expelled from the substrate. In this case, both of methoxy and hydroxy groups can be protonated and depart from the tetrahedral intermediate. However, the methoxy group is slightly

more basic than hydroxy group and therefore it is more likely to be removed than the hydroxy group. Moreover, in order to shift the equilibrium towards the product “carboxylic acid”, a large excess of water is used as a solvent.

$$EtC(O)OMe + H_2O \xrightleftharpoons[\text{Excess of } H_2O]{\text{Acid catalyst}} EtC(O)OH + MeOH$$

If the carboxylic acid produced is treated with a large excess of alcohol and heated, the reverse reaction would take place to give the corresponding ester.

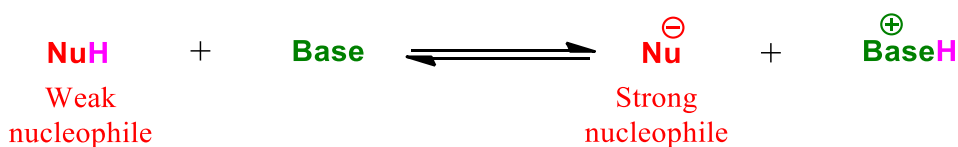
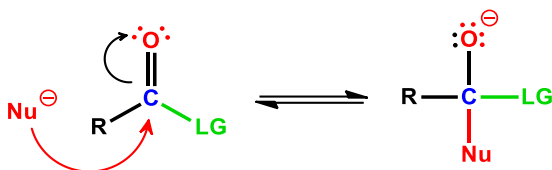
$$EtC(O)OH + EtOH \xrightleftharpoons[\text{Excess of EtOH, Heat}]{\text{Acid catalyst}} EtC(O)OEt + HOH$$

Base catalyzed reactions

Base catalyzed reactions consist in generating a stronger nucleophile. This process involves an acid-base reaction in which the nucleophile gets deprotonated by the base catalyst leading to the formation of the nucleophile conjugate base, which is more nucleophilic than its protonated form.

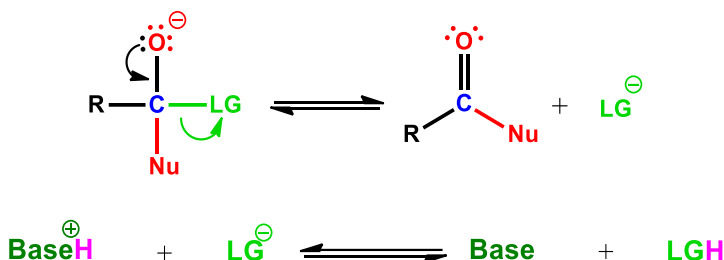
Step one

Formation of the nucleophile conjugate base.

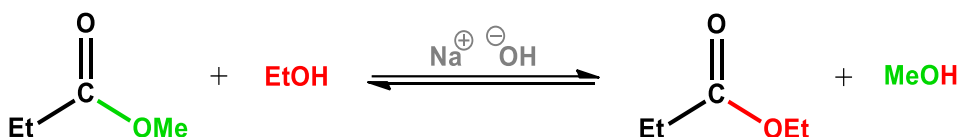
$$NuH + Base \rightleftharpoons Nu^{\ominus} + BaseH^{\oplus}$$

Weak nucleophile → Strong nucleophile

Addition of strong nucleophile to carbonyl carbon and formation of ionic tetrahedral intermediate.

Step two

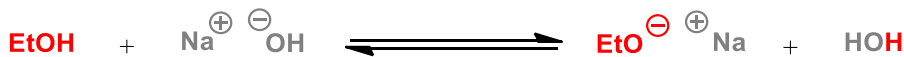
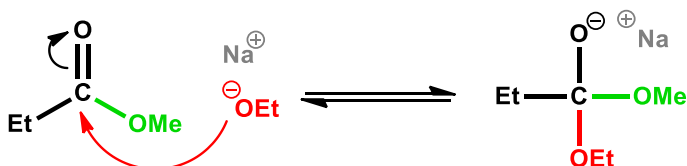
Reformation of carbonyl functional group and elimination of the nucleofuge.

$$BaseH^{\oplus} + LG^{\ominus} \rightleftharpoons Base + LGH$$

➲ ***Example***

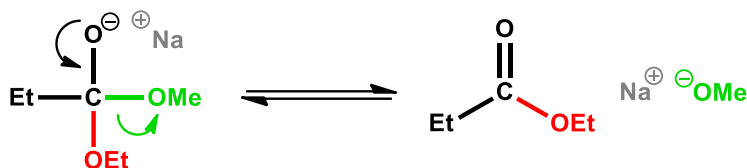
Transesterification is a re action that consists in changing the alkoxy group of an ester by another alkoxy group. Transesterification is a reversible reaction that involves an ester and alcohol in the presence of a base catalyst.

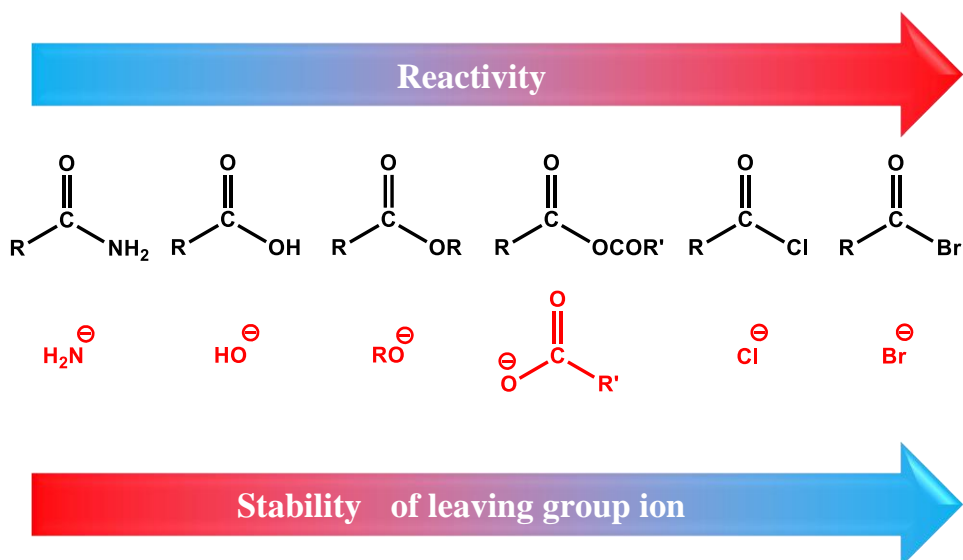
$$EtCOOMe + EtOH \xrightleftharpoons{Na^{\oplus}\ {}^{\ominus}OH} EtCOOEt + MeOH$$

Step one

Generation of strong nucleophile.

$$EtOH + Na^{\oplus}\ {}^{\ominus}OH \rightleftharpoons EtO^{\ominus}\ {}^{\oplus}Na + HOH$$

Addition of ethoxide ion to the carbonyl carbon.

Step two

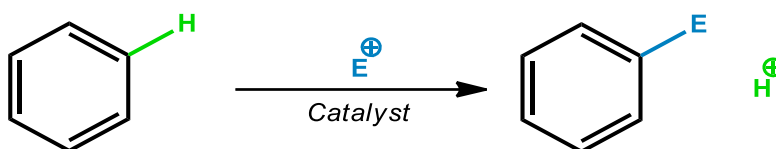
Elimination of methoxy group and reformation of the carbonyl function.

$$Et-C(O^{\ominus})(OEt)-OMe \; Na^{\oplus} \rightleftharpoons EtC(=O)OEt + Na^{\oplus} \; {}^{\ominus}OMe$$

Reactivity of Carboxylic Acids and their Derivatives

The reactivity of carboxylic acids and their derivatives towards nucleophiles varies from a compound to another according to the stability of the leaving group they contain. The most reactive compound is the one that releases the most stable nucleofuge. As a result, acyl halides rank the most reactive compounds in nucleophilic substitution reaction because halide ions are weak bases. The next reactive compounds are anhydrides for they release a resonance stabilized conjugate base. Esters are more reactive than carboxylic acids because alkoxides are more stable than the hydroxide ion due to the donating inductive effect of the alkyl group.

III. 1. 3. Electrophilic Substitution Reactions

III. 1. 3. 1. Electrophilic Aromatic Substitution Reactions S_EAr

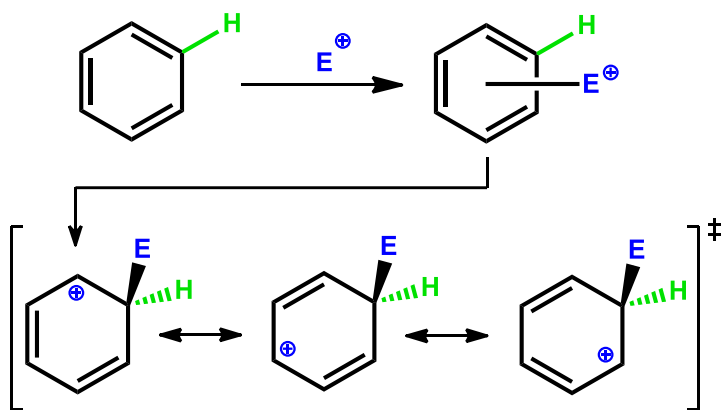
The vast majority of chemical reactions that aromatic compounds undergo are electrophilic substitution reactions whereby a hydrogen atom attached to the aromatic system gets replaced by an electrophile. At the course of an electrophilic aromatic substitution reaction, the aromatic ring acts as a Lewis base "electron donor" by providing the electrophile "electron-acceptor" with a pair of electrons in order to create a new σ bond. Moreover, because π bonds of the aromatic ring are involved in the aromatic system, they are not readily available to be shared with the electrophile. As a result, in most cases, electrophilic aromatic substitution reactions require the use of an appropriate catalyst in order to proceed.

$$C_6H_5H \xrightarrow[\text{Catalyst}]{E^{\oplus}} C_6H_5E + H^{\oplus}$$

Furthermore, electrophilic aromatic substitution reactions share one common mechanism known as S_EAr, which involves a carbocation intermediate "arenium ion". Nevertheless, depending upon the electrophile used, this mechanism may differ from one reaction to another.

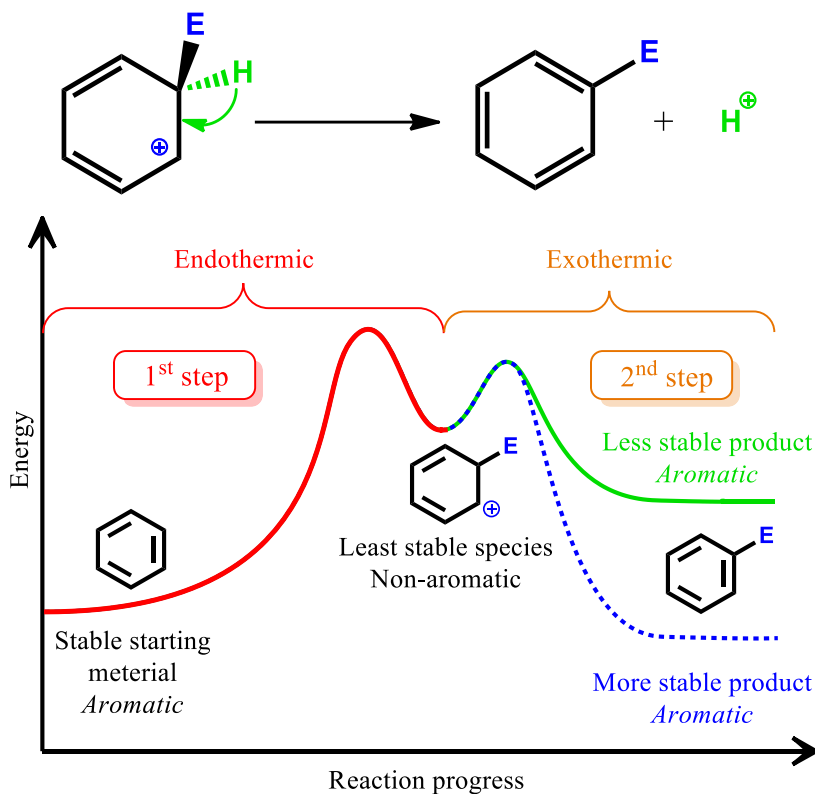
Mechanism

The general mechanism for an electrophilic aromatic substitution reaction proceeds in two steps.

Step one

In the first step, the aromatic compound donates one pair of electrons to the electrophile creating, this way, a new σ bond with it. This process results in the loss of the aromaticity of the starting material and the formation of a carbocation intermediate known as σ complex or *Wheland* intermediate, which is resonance stabilized. Since the carbocation intermediate formed is less stable than the aromatic starting material, this step is a slow endothermic process.

Wheland intermediate

Step two

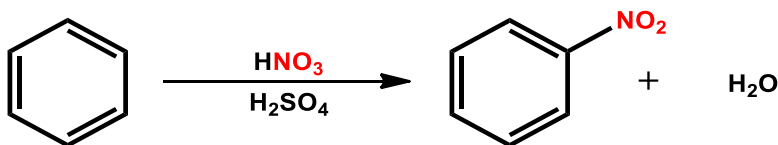
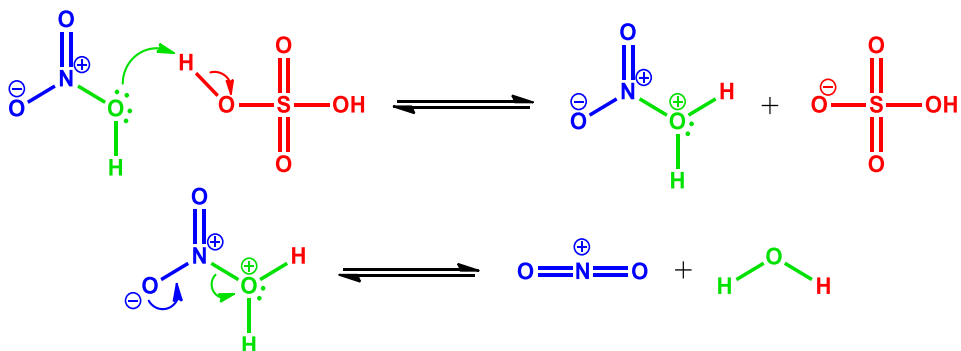
The second step is a fast exothermic process characterized by the elimination of the electrofuge H^+ and restoration of compound aromaticity. At this point, a base would abstract a hydrogen proton fromthe carbon atom attached to the electrophile, which leads to the formation of a new π bond. Moreover, the final product can either be more stable than the starting material or less stable based on the nature of the electrophile used.

Common Reactions

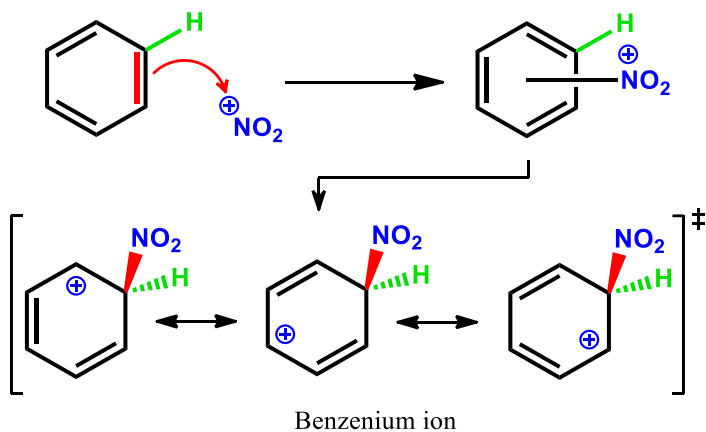
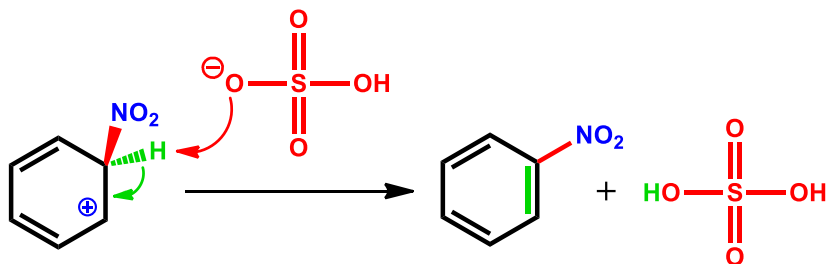
Electrophilic aromatic substitution reactions can be classified into five main categories "shown in the table below" depending upon the electrophile used. These reactions allows chemists to introduce new functional groups on aromatic compounds, which can be used for further organic syntheses.

Reaction	Reagents	Electrophile	Product
Nitration	HNO_3 : H_2SO_4	NO_2	Ar-NO2
Sulfonation	SO_3 : H_2SO_4	SO_3	Ar-SO3H
Halogenation	X_2 : AlX_3 or FeX_3	X	Ar-X
Alkylation	RCl : AlX_3 or FeX_3	R	Ar-R
Acylation	RCOCl : AlX_3 or FeX_3	RCO	Ar-COR

Nitration

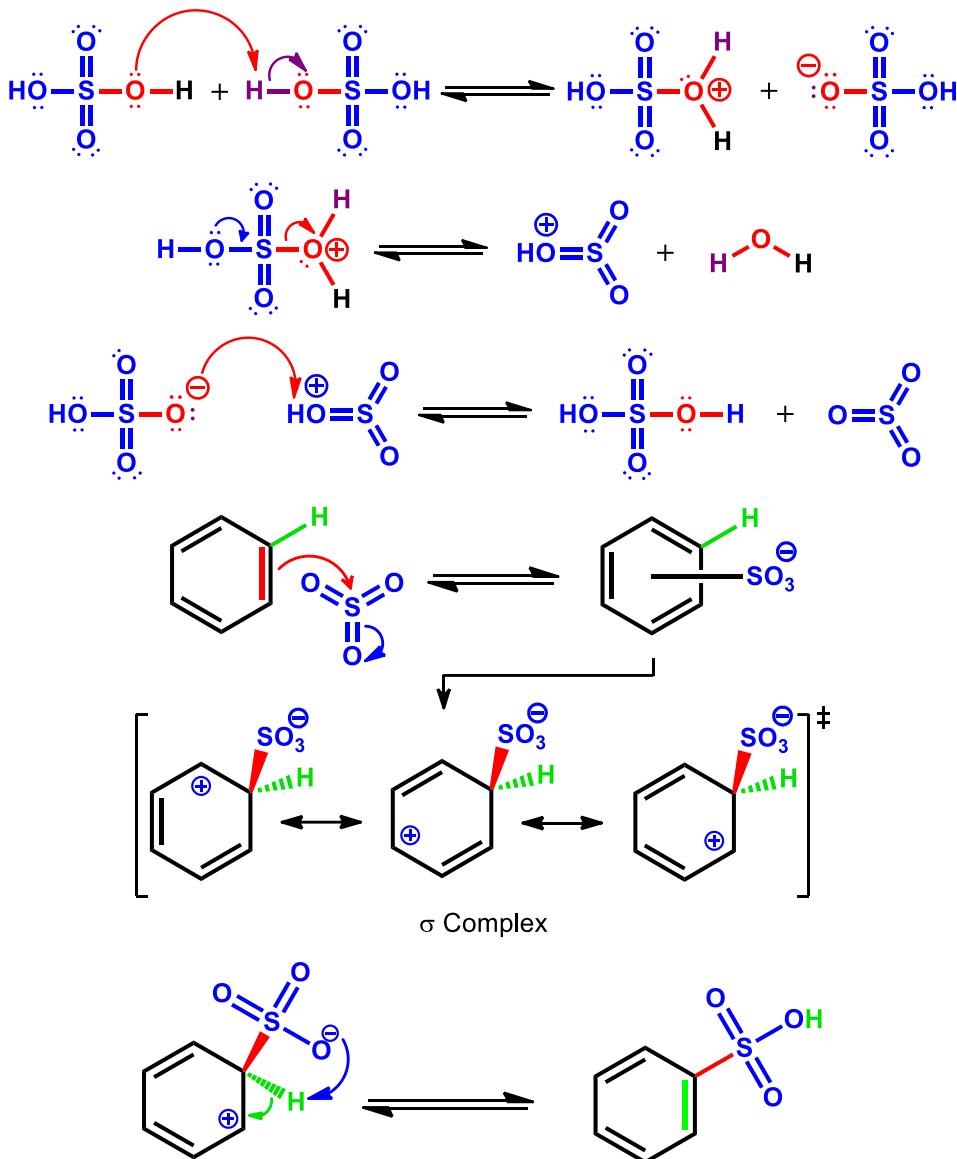
Nitration reaction is the introduction of nitro group NO_2 into an aromatic substrate. In this reaction, the substrate is treated with concentrated nitric and sulfuric acids.

$$C_6H_6 \xrightarrow[H_2SO_4]{HNO_3} C_6H_5NO_2 + H_2O$$

Concentrated sulfuric acid H_2SO_4 reacts with concentrated nitric acid HNO_3 to give the electrophilic nitronium ion NO_2^+. In this case, because nitric acid HNO_3 ($pK_a \approx$ -1.4) is weaker than sulfuric acid H_2SO_4 ($pK_a \approx$ -3), it acts as a base while sulfuric acid acts as an acid.

By the time nitronium ion forms, it gets captured by the aromatic bond resulting in the formation of an arenium ion "benzenium ion for benzene", which is stabilized by resonance effect.

Benzenium ion

The next step involves the abstraction of a hydrogen proton "electrofuge" by a base "conjugate base of sulfuric acid or water", which gives rise to the final aromatic compound.

Sulfonation

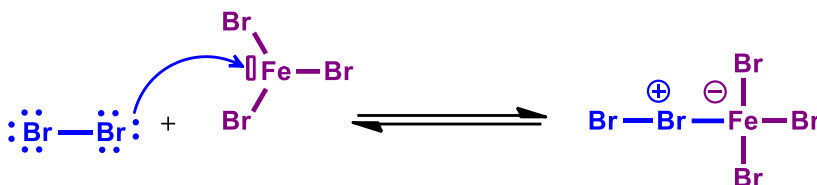
Sulfonation of aromatic rings is an electrophilic reaction that consists in replacing a hydrogen atom with sulfonic acid in order to produce arenesulfonic acids. The most effective method for this reaction is using ***oleum***, which is a solution of sulfur

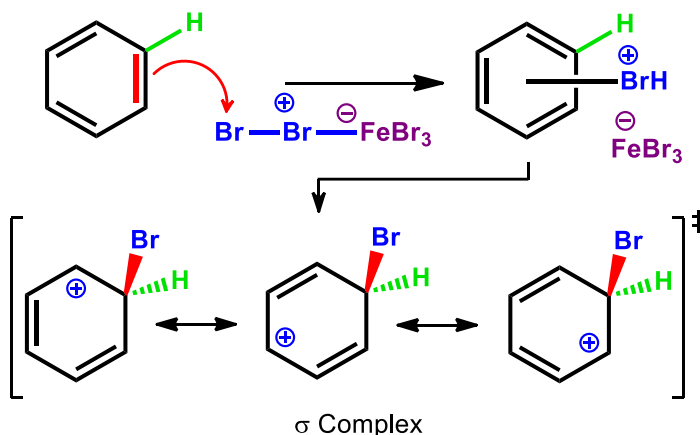
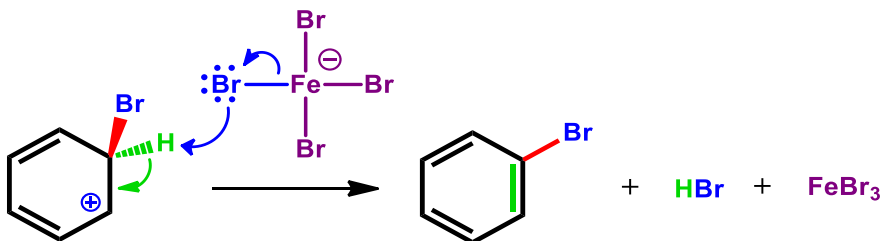
trioxide SO_3 in concentrated sulfuric acid H_2SO_4. Sulfonation reaction proceeds in two reversible steps. In a c oncentrated sulfuric acid , the equilibrium is shifted towards the sulfonic acid. However, under heat and in aqueous dilute sulfuric acid, the opposite is true.

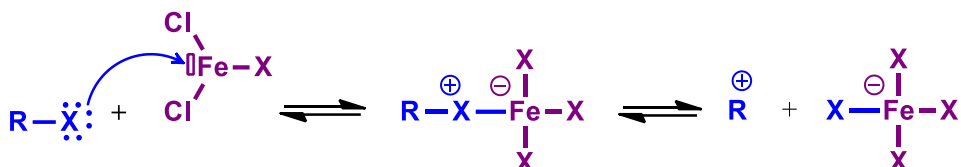
σ Complex

Halogenation

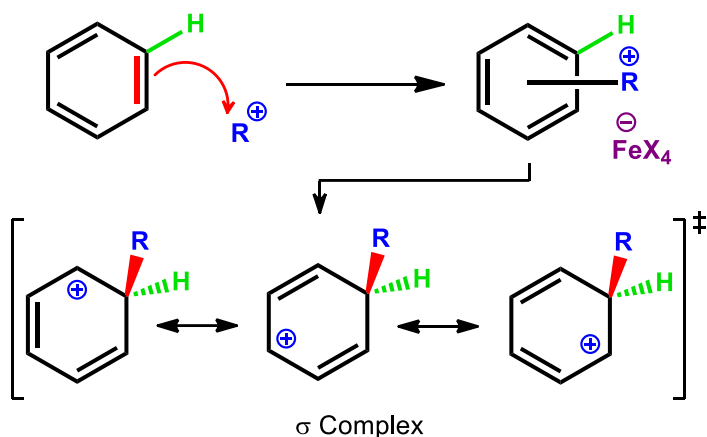
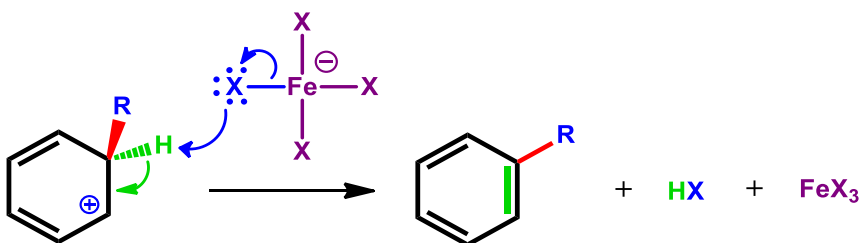
Halogenation of aromatic compounds describes the reaction whereby a hydrogen atom gets displac ed by a halogen atom such as chlorine and bromine. Because dihalogens are not sufficiently electrophilic to react with the weak nucleophile

“aromatic substrate”, it is necessary to use a Lewis acid catalyst such as aluminum trihalides **AlX_3** or iron trihalid es **FeX_3**, where **X** is bromine for bromination or chlorine for chlorination. Nevertheless, some aromatic compounds such as phenol and aniline do not require Lewis acid catalysts.

Halogenation of aromatic compounds proceeds in three steps. Initially, the dihalogen molecule reacts with the Lewis acid catalyst to form a Lewis acid -base complex in order to generate the electrophilic halogen.

The next step consists in the addition of the electrophile to the aromatic ring, which leads to the formation of *Wheland* intermediate.

σ Complex

The final step is a fast exothermic process where aromaticity is restored after the abstraction of a hydrogen p roton from the arenium ion. In this reaction , the final product is more stable than the starting material because halogens are deactivating group.

Alkylation

Alkylation of aromatic compounds consists in displacing a hydrogen atom with an alkyl group. This reaction can be accomplished via *Friedel–Crafts alkylation*, which involves an alkyl halide in the presence of a Lewis acid catalyst such as AlX_3 or FeX_3 to proceed. Friedel–Crafts alkylation proceeds in three steps. Initially, the alkyl halide reacts with the Lewis acid to form a Lewis acid-base complex, which then collapses leaving the alkyl residue with a positive charge (electrophile).

Later on, the electrophilic alkyl adds to the aromatic ring resulting in a σ complex.

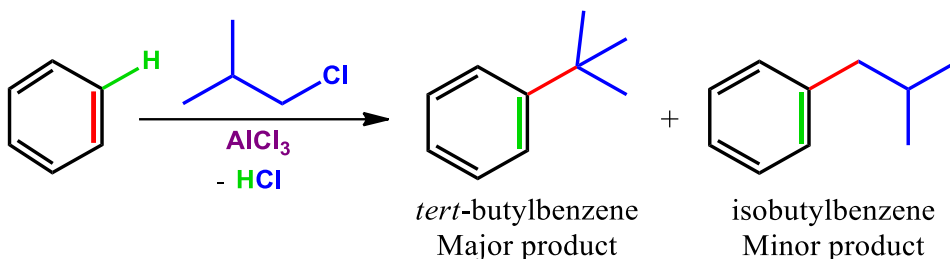
σ Complex

The final step consists in eliminating the hydrogen proton attached the carbon atom to which the alkyl has been added. This process will then lead to the final aromatic compound.

In general, Friedel–Crafts alkylation evolves rearrangement of the alkyl group whereby the most stable electrophile adds to the aromatic ring.

➲ ***Example***

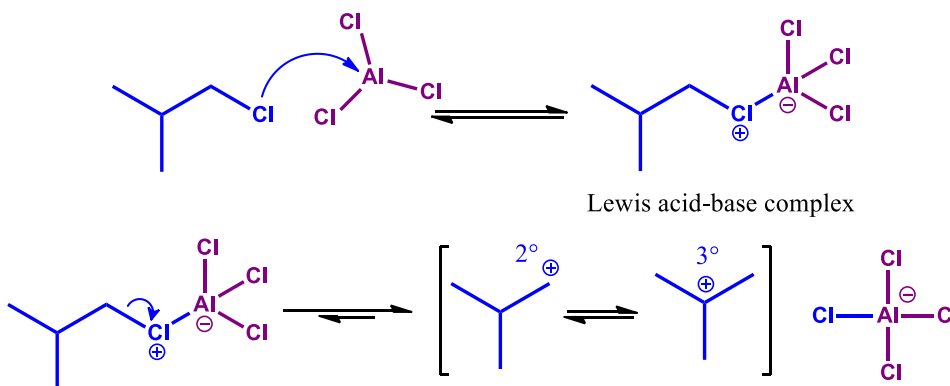
Alkylation of benzene with 1-chloro-2-methylpropane in the presence of aluminum trichloride $AlCl_3$ gives two products with one predominant isomer.

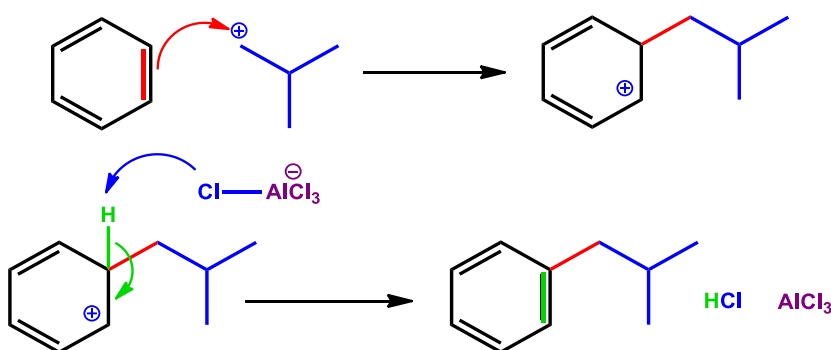
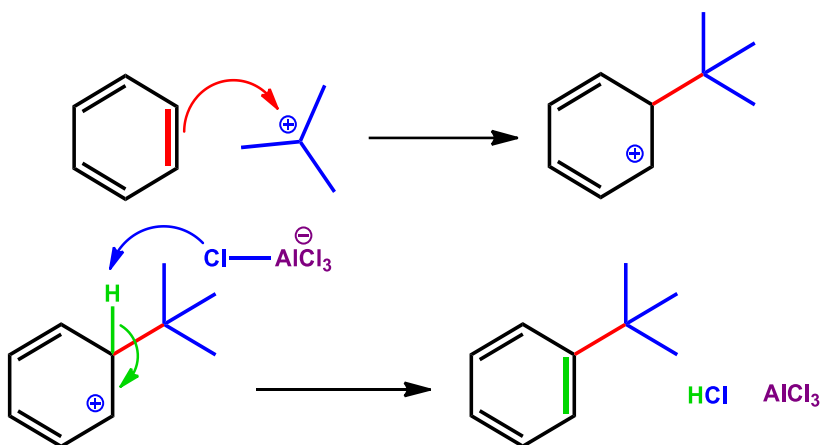
H
Cl
$AlCl_3$
- HCl
+

tert-butylbenzene
Major product

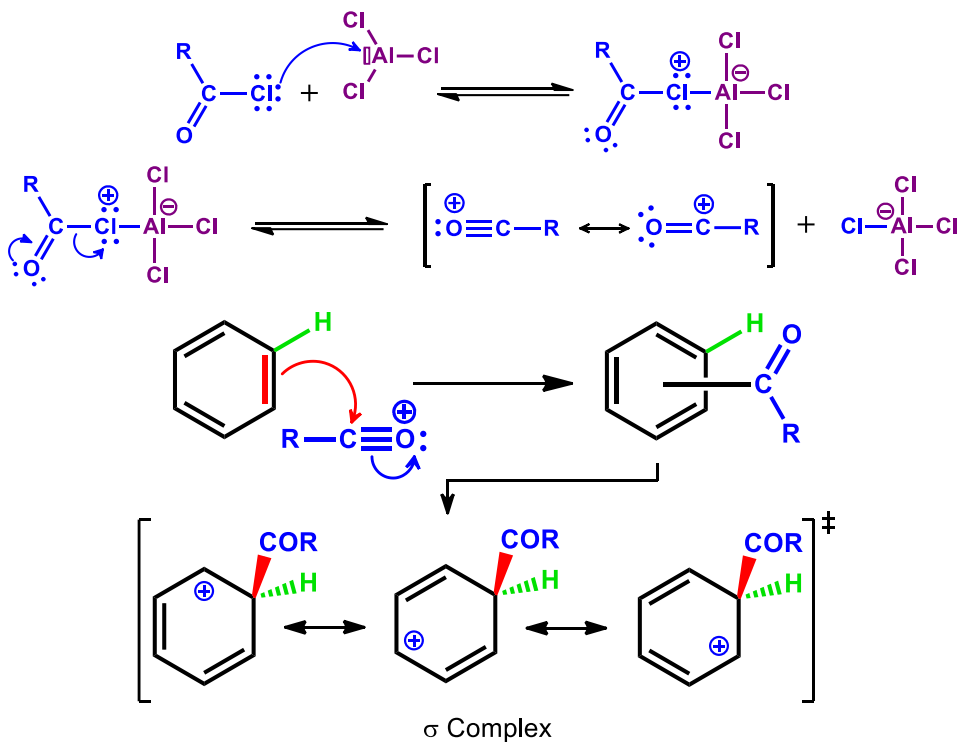
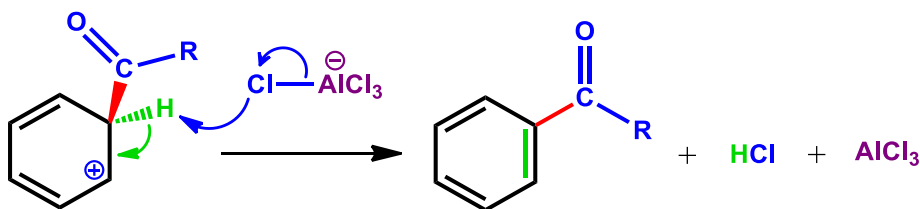
isobutylbenzene
Minor product

Because $AlCl_3$ is a strong Lewis acid, the dissociation of Lewis acid-base complex shifts towards the carbocation and tetrachloroaluminate $AlCl_4^-$. In this case, the secondary carbocation intermediate formed can attain a more stable state via 1,2 - hydride shift.

Lewis acid-base complex

2° 3°

As a result, there would be two possible electrophiles, with which the aromatic ring can react. Nevertheless, because tertiary carbocation is more stable than secondary, the reaction would yield more *tert*-butylbenzene than isobutylbenzene.

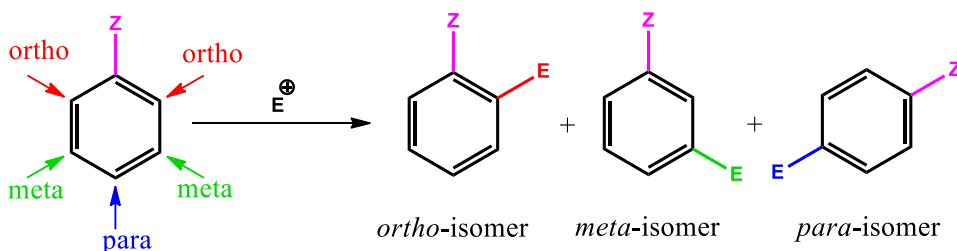
HCl AlCl₃

Acylation

Friedel–Crafts acylation is the reaction whereby an acyl group displaces a hydrogen atom of an aromatic ring . This particular reaction involves an acyl halide, which generates the electrophile upon reaction with a Lewis acid catalyst and it proceeds in similar way to Friedel–Crafts alkylation.

σ Complex

Regioselectivity

Mono-substituted Benzenes

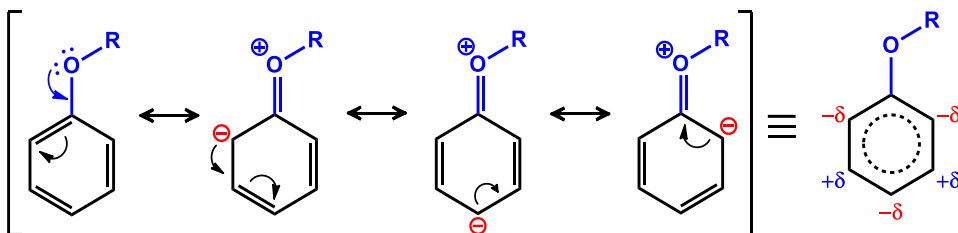
When a mono-substituted benzene C_6H_5Z undergoes an S_EAR reaction, the electrophile can be added to different positions of the aromatic ring. In this case, the reaction outcome would either be exclusive, to nearly so, *meta* isomer or a mixture of *ortho* and *para* isomers. The regioselectivity of such reactions depends upon the nature of the substitute Z and it can be explained by *Holleman's rule*.

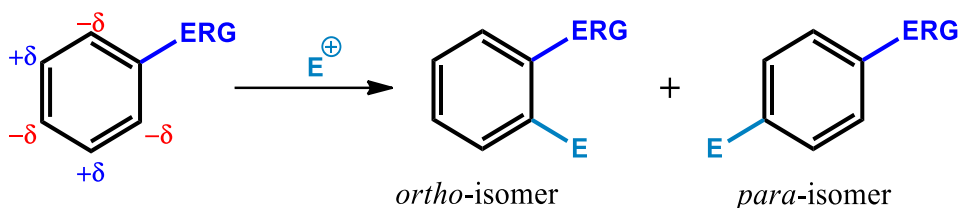
ortho-isomer *meta*-isomer *para*-isomer

Holleman's Rule

According Holleman's rule, an electron-releasing group is an activating group that directs electrophilic substitution towards *ortho*- and *para* positions with the para orientation being generally more favorable. On the other hand, an electron-withdrawing group is a deactivating *meta*-directing group except for halogens, which are deactivating, *ortho*- and *para*-directing groups.

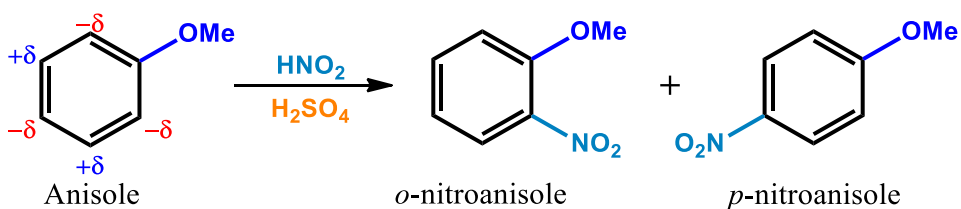
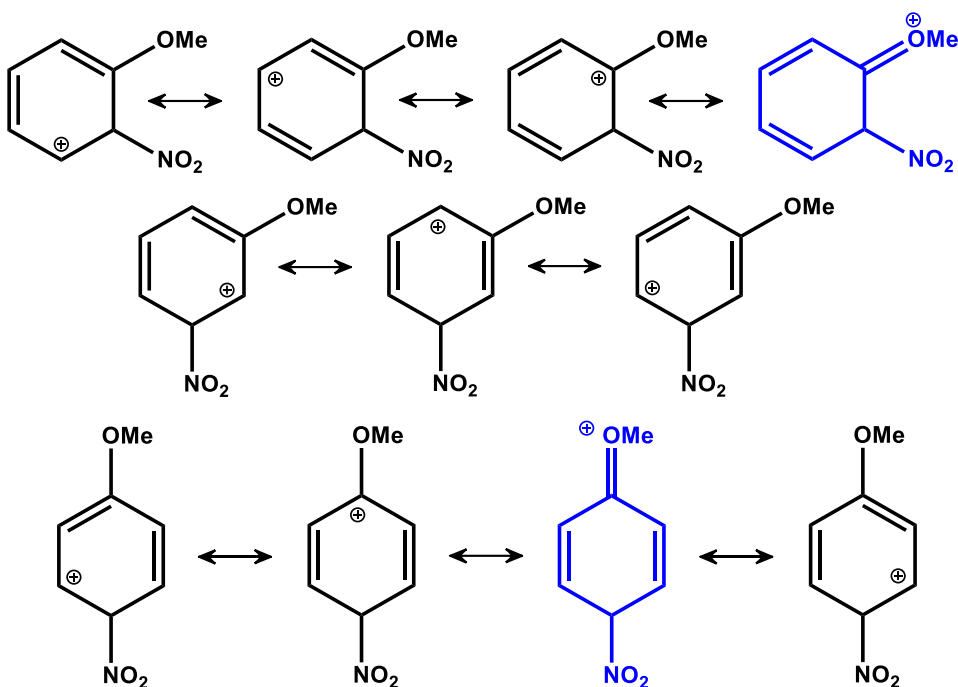
Activating Groups

Activating groups are electron-releasing groups ERG that helps in optimizing the aromatic compound nucleophilicity. Electron -releasing groups increase electron density of the aromatic ring via donating mesomeric $+M$ or donating inductive effect $+I$ and therefore, making it more reactive towards electrophiles. In the example below, the alkoxy group is an activating group where it provides the aromatic ring with additional electron density via $+M$. In this case, the negative

charge is delocalized by resonance effect and it can be located in two main positions with respect to the methoxy group, ortho and para.

As a result, *ortho* and *para* positions are more nucleophilic than *meta* positions and thus, electrophilic substitution is more likely to take place there. However, *para* isomer will generally predominate over ortho-isomer.

ortho-isomer *para*-isomer

➲ ***Example***

Nitration of anisole gives a mixture of nitroanisole isomers.

Anisole $\xrightarrow[H_2SO_4]{HNO_2}$ *o*-nitroanisole + *p*-nitroanisole

The regioselectivity of this reaction is also related to *Wheland* intermediate stability. If the electrophile adds to the *ortho* or *para* positions, four resonance contributors are possible with one more stabilized contributor "shown in blue". On the other hand, when the electrophile adds to *meta* position, only three resonance contributors are possible.

The following table shows common activating groups.

Substituent	Electronic effect	Regioselectivity	Strength
$-O^{\ominus}$	$+I$ $+M$	Ortho Para	Strong
$-NH_2$	$-I$ $+M$		
$-NHMe$			
$-N(Me)_2$			
$-OH$			
$-OMe$			
$-SH$			Moderate
$-SMe$			
$-Ph$			Weak
$-CHCH_2$			
$-R$	$+I$		

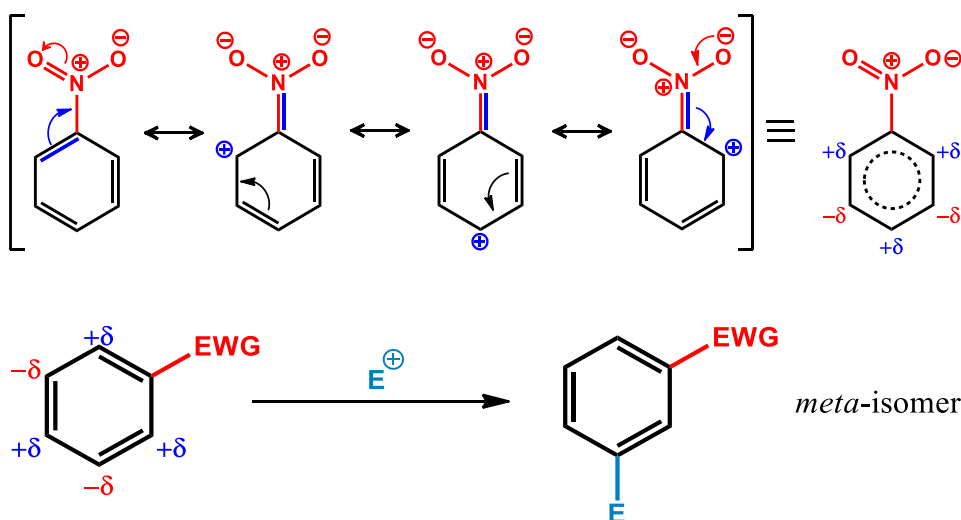
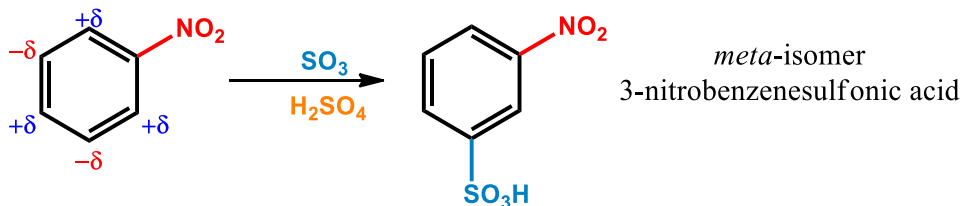
Deactivating Groups

Deactivating groups are electron-withdrawing groups EWGs that decrease electron density of the aromatic ring via withdrawing mesomeric effect –*M* and withdrawing inductive effect –*I*, which makes the aromatic substrate less reactive towards electrophiles. In the example below, the nitro group is a deactivating group where it pulls away a π bond from the aromatic ring via withdrawing mesomeric effect –*M*. This process will result in the formation of a positive charge on the ring, which can be delocalized on two main positions with respect to the nitro group, *ortho* and *para*. In this case, *ortho* and *para* positions have less electron density than the *meta* position and therefore the electrophile is more likely to add to the *meta* potion, which is the most nucleophilic position.

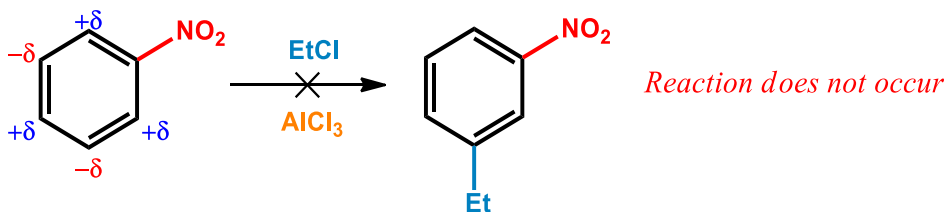
$\xrightarrow{E^{\oplus}}$ *meta*-isomer

➲ ***Example***

$\xrightarrow[H_2SO_4]{SO_3}$

meta-isomer
3-nitrobenzenesulfonic acid

⊗ Note: In case of strongly deactivated arenes likes nitrobenzene, it is important to know that Friedel-Craft alkylation is not possible.

$-\delta$, $+\delta$, $+\delta$, $-\delta$, $+\delta$ ... NO_2 $\xrightarrow[AlCl_3]{EtCl}$ (crossed arrow) NO_2, Et

Reaction does not occur

The following table shows common deactivating groups and their directing effects.

<table>
<tr><th>Substituent</th><th>Electronic effect</th><th>Regioselectivity</th><th>Strength</th></tr>
<tr><td>—SO_2CF_3</td><td>$-I$ $-M$</td><td rowspan="13">Meta</td><td rowspan="7">Strong</td></tr>
<tr><td>—$\overset{\oplus}{N}(Me)_3$</td><td>$-I$</td></tr>
<tr><td>—NO_2</td><td rowspan="4">$-I$ $-M$</td></tr>
<tr><td>—SO_3H</td></tr>
<tr><td>—SO_2Me</td></tr>
<tr><td>—CN</td></tr>
<tr><td>—CX_3
X = F, Cl, Br, I</td><td>$-I$</td></tr>
<tr><td>—C(O)X</td><td rowspan="6">$-I$ $-M$</td><td rowspan="6">Moderate</td></tr>
<tr><td>—C(O)H</td></tr>
<tr><td>—C(O)Me</td></tr>
<tr><td>—C(O)OH</td></tr>
<tr><td>—C(O)OMe</td></tr>
<tr><td>—$C(O)NH_2$</td></tr>
<tr><td>—F</td><td rowspan="2">$-I$ $+M$</td><td>Para</td><td rowspan="2">Weak</td></tr>
<tr><td>—X
X = Cl, Br</td><td>Ortho
Para</td></tr>
</table>

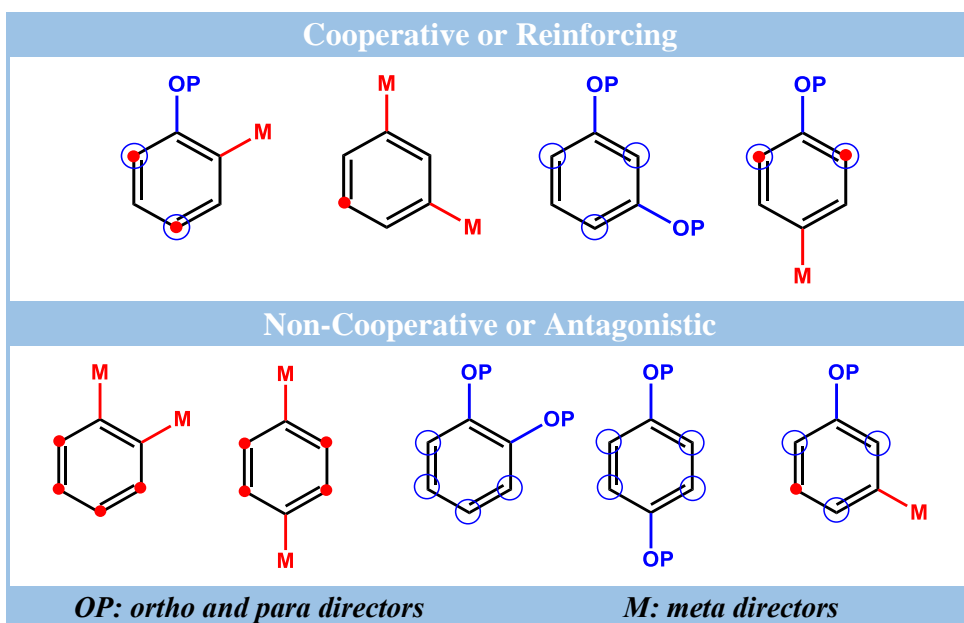
Disubstituted Benzenes

When a disubstituted benzene undergoes an electrophilic aromatic substitution reaction, each substituent exerts an influence over reaction rate and regioselectivity. In other words, the position to which the electrophile adds depends upon the sum of the directing effects of both substituents and which one is stronger. For that, substituents can be classified into classes; cooperative systems and non-cooperative systems.

In case of cooperative systems, determining the position at which the electrophilic substitution will take place is more predictable because the directing effects of both substituents intersect at the same positions. On the other hand, in non-cooperative systems the directing effects of each substituent do not intersect. In this case, each substituent should be examined based on its strength and steric hindrance.

Cooperative or Reinforcing

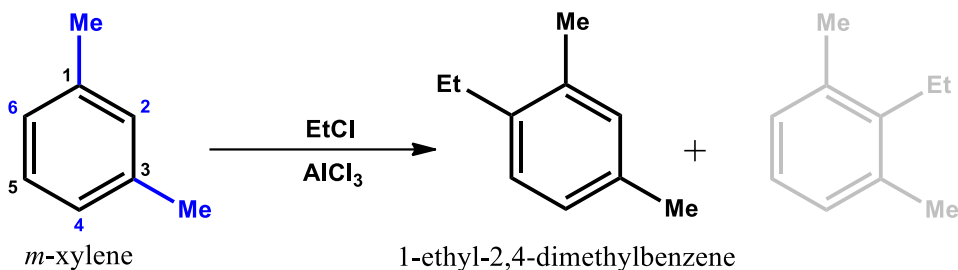
Non-Cooperative or Antagonistic

OP: ortho and para directors ***M: meta directors***

Cooperative systems

Alkylation of *m*-xylene with ethyl chloride and aluminum trichloride catalyst gives 1-ethyl-2,4-dimethylbenzene. In this case, the electrophile "ethyl" adds to carbon 4 or 6 because carbon 2 is more sterically hindered.

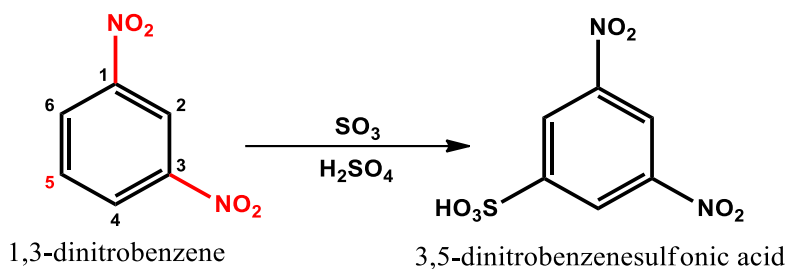
$\xrightarrow[AlCl_3]{EtCl}$

m-xylene

1-ethyl-2,4-dimethylbenzene

Sulfonation of 1,3-dinitrobenzene produces 3,5-dinitrobenzenesulfonic acid where sulfonic acid adds to carbon 5 because it is the only available position.

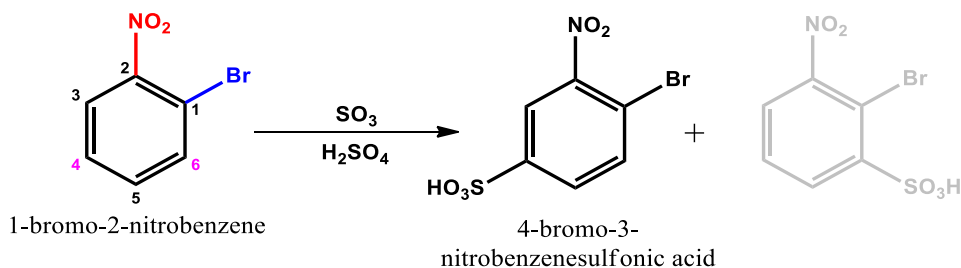
$\xrightarrow[H_2SO_4]{SO_3}$

1,3-dinitrobenzene

3,5-dinitrobenzenesulfonic acid

Sulfonation of 1-bromo-2-nitrobenzene would produce two isomers with 4-bromo-3-nitrobenzenesulfonic acid at higher rate because position 6 is somewhat disfavored due to the steric hindrance.

$\xrightarrow[H_2SO_4]{SO_3}$

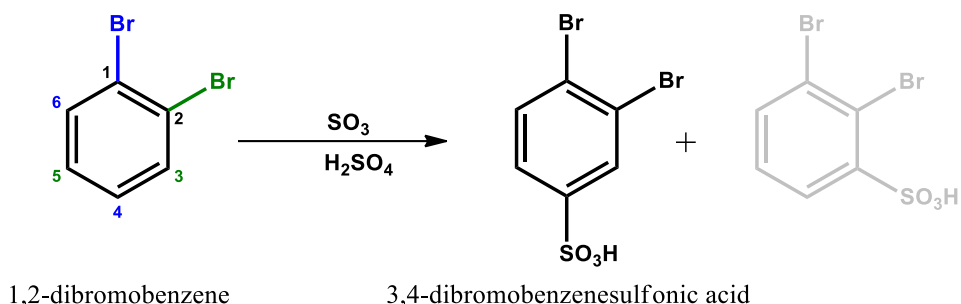
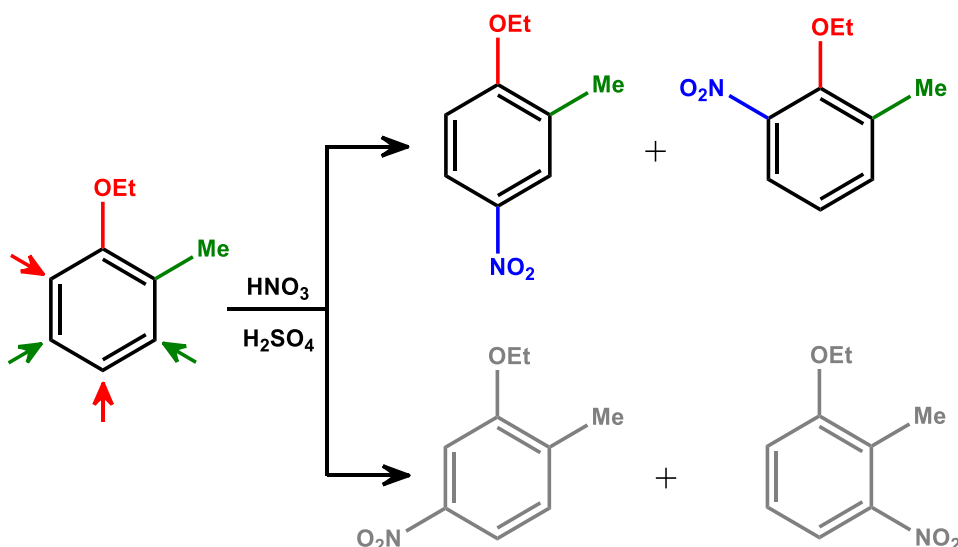
1-bromo-2-nitrobenzene

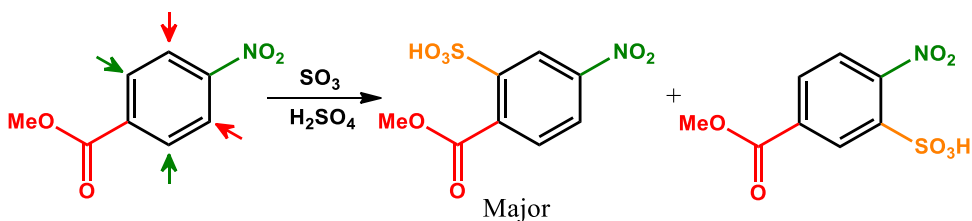
4-bromo-3-nitrobenzenesulfonic acid

Non-cooperative systems

For non-cooperative systems, three factors can help in predicting the position where electrophilic substitution is more likely to occur.

- The stronger substituent predominates over the weaker one in determining the regioselectivity of the reaction.
- Mesomeric effect is always stronger than the inductive effect.
- Electrophiles tend to add to the least hindered position.

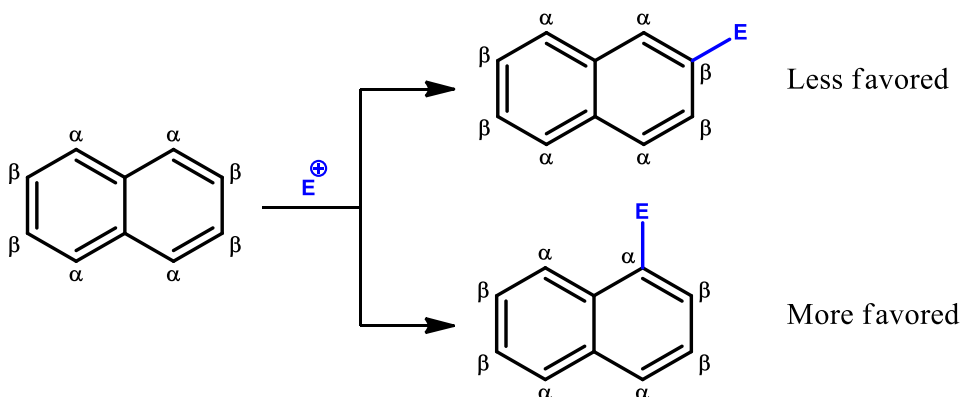
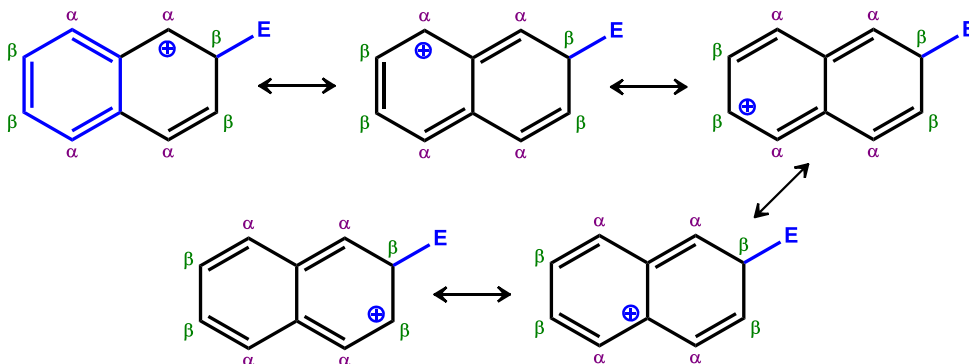
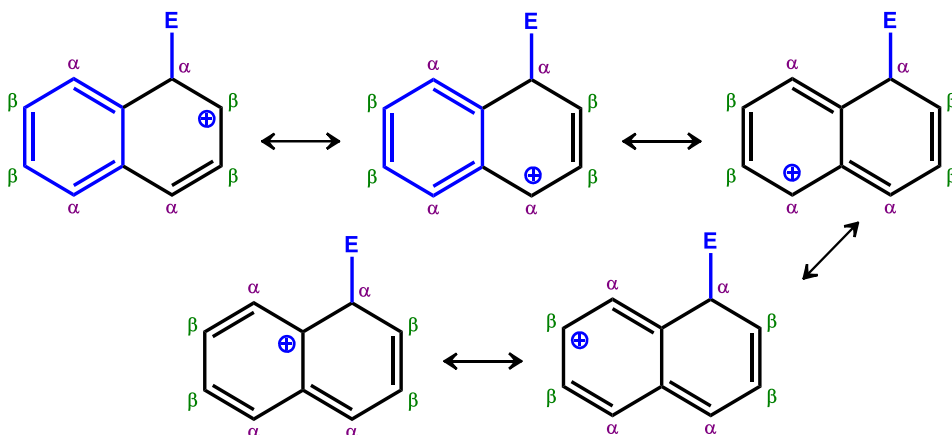
Sulfonation of 1,2 -dibromobenzene gives 3,4-dibromobenzenesulfonic acid as a major product because position 3 and 6 are more sterically hindered than position 4 and 5. In this case, because both substituents are identical, the reaction will give the same product whether the electrophile adds to carbon 4 or 5.

1,2-dibromobenzene 3,4-dibromobenzenesulfonic acid

In case of non-identical substituents on position 1 and 2, all potential isomers may form where priority goes to the stronger substituent and the electrophile adds to the least hindered position. For example, nitration of 1-ethoxy-2-methylbenzene may give four isomers where two of them are predominant. In this case, because ethoxy group is stronger than methyl, nitration is more likely to take place at the positions determined by the ethoxy group.

In next example, both substituents are deactivating, meta-directing groups. In this case, priority goes to nitro group because its electron -withdrawing effect *–M* is stronger than the electron -withdrawing effect *–M* of the carbonyl. As a result, sulfonation will take place at position *meta* with respect to the nitro group.

Major

Polycyclic Arenes "Naphthalene"

Electrophilic aromatic substitution of naphthalene is more likely to occur at the α–position than the β–position. The reason behind this is the stability of the arenium ion intermediate for each case.

Less favored

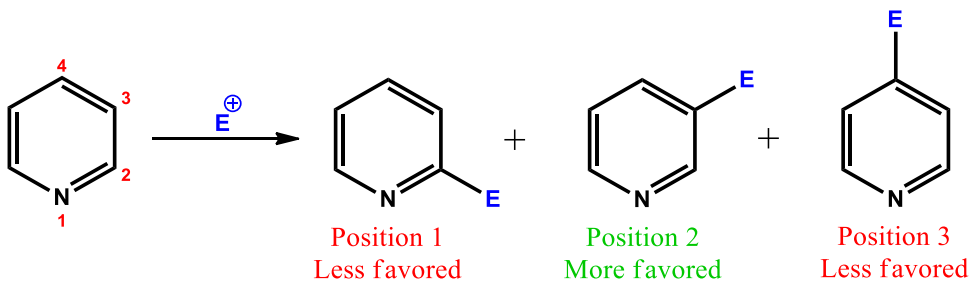
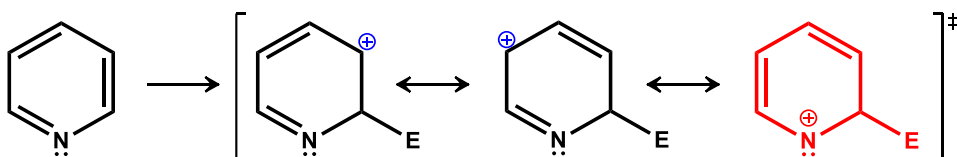
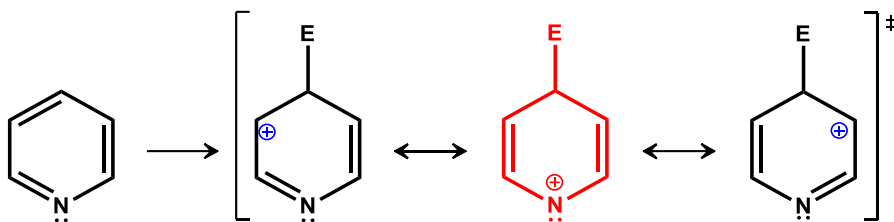
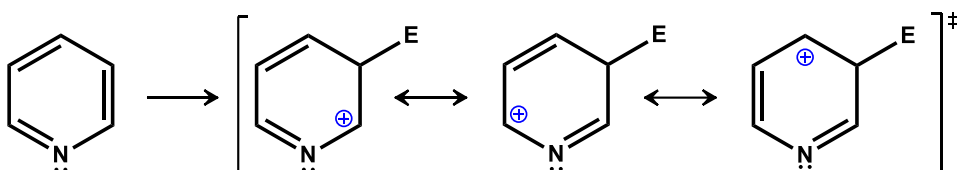
More favored

When the electrophile adds to the position α, the arenium ion intermediate will have five resonance contributors with two forms having a full aromatic ring. In contract, when the electrophile adds to the β position, only one resonance contributor will have a full aromatic ring. As a result, α position is more reactive towards electrophiles than β position.

Heteroaromatic Compounds

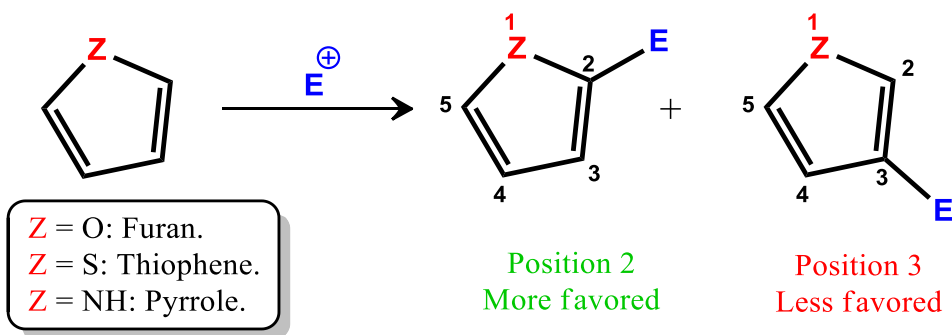
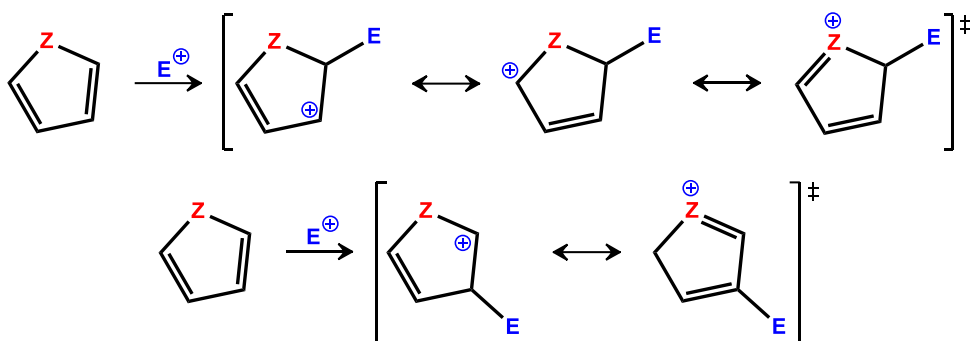
Pyridine

Pyridine is a six membered heteroaromatic compound that possesses an sp^2 nitrogen atom. When this compound undergoes an electrophilic substitution reaction, the electrophile is more likely to add to position 2.

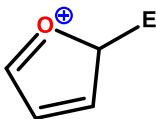
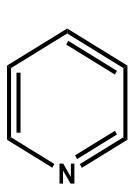
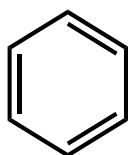
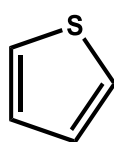
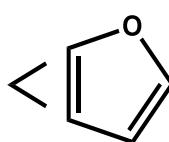
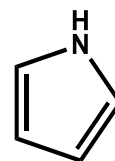
Position 1
Less favored

Position 2
More favored

Position 3
Less favored

This regioselectivity is determined by which position will generate the most stabilized pyridinium ion intermediate. In all cases, the pyridinium ion has three resonance contributors. However, when the electrophile adds to position 1 or 3, one resonance contributor will be unstable because the positive charge will be located on a nitrogen atom that does not have a fully saturated valence.

On the other hand, when the electrophile adds to position 2, the positive charge will be distributed between three carbon atoms , which makes this pyridinium ion the most stable one.

Furan, Pyrrole, Thiophene

Electrophilic aromatic substitution reaction is more favorable at position 2 than 3 in five membered heteroaromatic compounds such as furan, pyrrole, and thiophene. This regioselectivity is determined by the stability of the in termediate formed in each case.

If the electrophile adds to the position 2, three resonance contributors will stabilize the intermediate formed. On the other hand, when the electrophile adds to the position 3, only two resonance contributors are possible, which makes position 2 more favorable than position 3.

Reactivity

In case of heteroaromatic compound, the nature of the heteroatom does affect the overall rate of reaction by making the aromatic ring more or less reactive. The reactivity of a heteroaromatic compound is related to the stability of its arenium ion.

	Benzenium ion is more stable than pyridinium ion because sp^2 hybridized carbocation is more stable than nitrogen cation, which does not obey the octet rule. Here, the nitrogen atom in pyridine acts as a deactivating group. As a result, benzene is more reactive towards electrophiles than pyridine.
	Thiophenium ion is more stable than pyridinium ion because in contrast to nitrogen cation, sulfur cation does obey the octet rule. As a result, thiophene is more reactive than pyridine.
	Furanium ion is more stable than thiophenium ion because electron lone pairs of sulfur belong to 3p orbitals, which makes them less effective to overlap with 2p electrons of the sp^2 aromatic carbon atom. Oxygen lone pairs, on the other hand, are more prone to overlap with the aromatic p orbitals.

>	Pyrrolium ion is more stable than furanium ion due to the diffe rence in electronegativity. Because nitrogen is less electronegative than oxygen, it forms a more stable cation than the oxygen.

Pyridine < Benzene < Thiophene < Furan < 1*H*-pyrrole

Reactivity towards Electrophiles

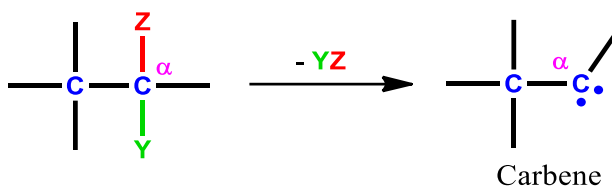
III. 2. Elimination Reactions

Elimination reactions consists in removing two groups Y and Z from within a substrate. In most cases, Y is a hydrogen atom whereas Z is an electron-withdrawing group such as a halogen or hydroxy group. These two species can be attached to the same atom of the substrate or to different atoms. As a r esult, elimination reactions can be classified into three main categories depending upon the positions of Y and Z.

- 1,1-elimination or α–elimination.
- 1,2-elimination or β–elimination.
- 1,3-elimination or γ–elimination.

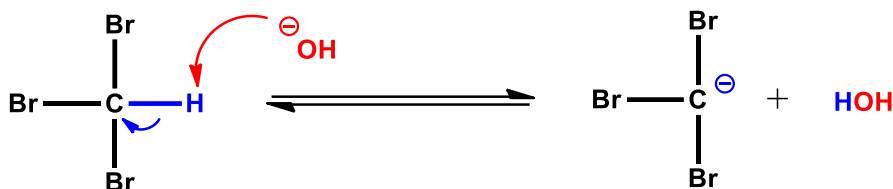
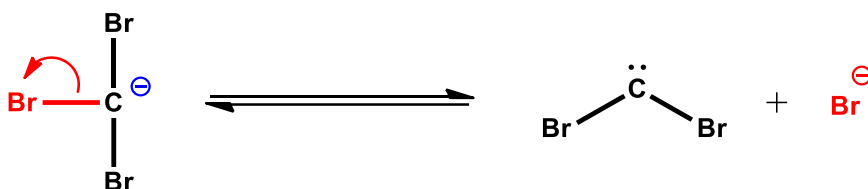
III. 2. 1. α – Elimination Reactions

α–elimination reaction, also known as 1, 1 – elimination, describes the reaction in which both leaving groups Y and Z are removed from the same atom. This particular reaction generally leads to the formation of a carbene or nitrene, which are reactive species used in further reactions.

Z
α
C C
Y
- YZ
α
C C
Carbene

III. 2. 1. 1. Formation of Carbenes

The most common procedure to generate carbene species is throughα–elimination. This reaction occurs with haloforms such as chloroform $CHCl_3$, and bromoform $CHBr_3$ when they are treated with a strong base. Because of the withdrawing inductive effect of the three halogens,the carbon-hydrogen bond is highly polarized and thus, acidic. As a result, when a base such as, NaOH or *t*-buOK, is introduced to the compound, an α–elimination reaction would take place whereby a hydrogen and halogen get removed.

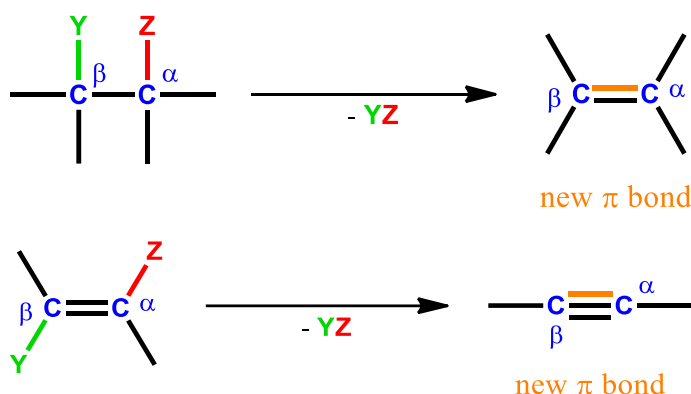
Mechanism

This reaction proceeds in two steps. At first, the base abstract the acidic hydrogen from the haloform resulting in a carbanion intermediate.

Later on, a halogen would leave the substrate taking away the bonding electron, which leaves the carbon with 6 valence electrons. At this point, a dihalogen carbene is formed.

This particular carbene can then react with another compound such as alkene to give the corresponding 1,1-dibromocyclopropane (*page 176*).

III. 2. 2. β – Elimination Reactions

β–elimination reactions, also known as 1, 2 –elimination reactions, are the most common type of elimination reactions. In this case, the leaving groups Y and Z are adjacent to one another and as they get removed from the substrate, a new π bond forms between the two carbon atoms to which Y and Z were attached resulting in the formation of an alkene or alkyne.

new π bond

new π bond

Moreover, depending upon the substrate structure and the re action conditions . β–elimination reactions are further subdivided into three types; unimolecular elimination E1, unimolecular conjugate base elimination E1cB, and bimolecular elimination E2.

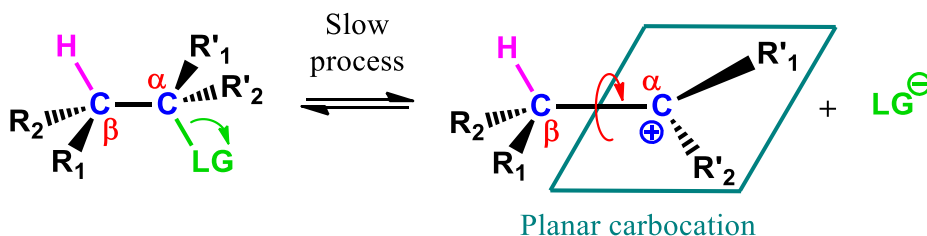
Unimolecular Elimination Reactions E1

Unimolecular elimination reaction E1 is a first order reaction that proceeds in two steps and involves an ionic intermediate.

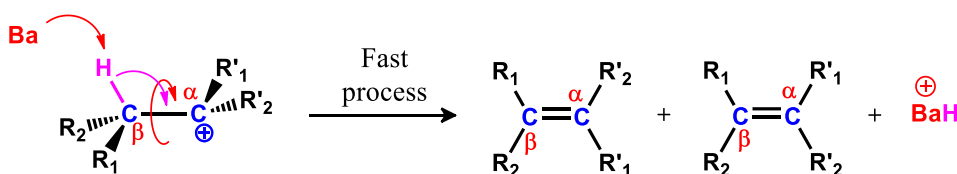
Step one

The first step is a slow reversible process wherebythe bond connecting the leaving group to the substrate breaks resulting in a carbocation intermediate.

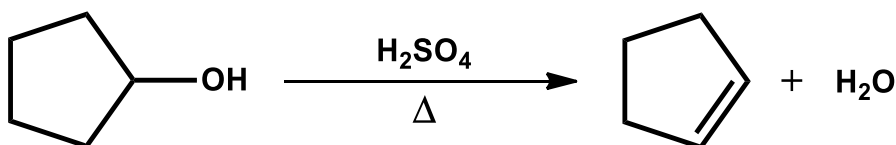
Slow process

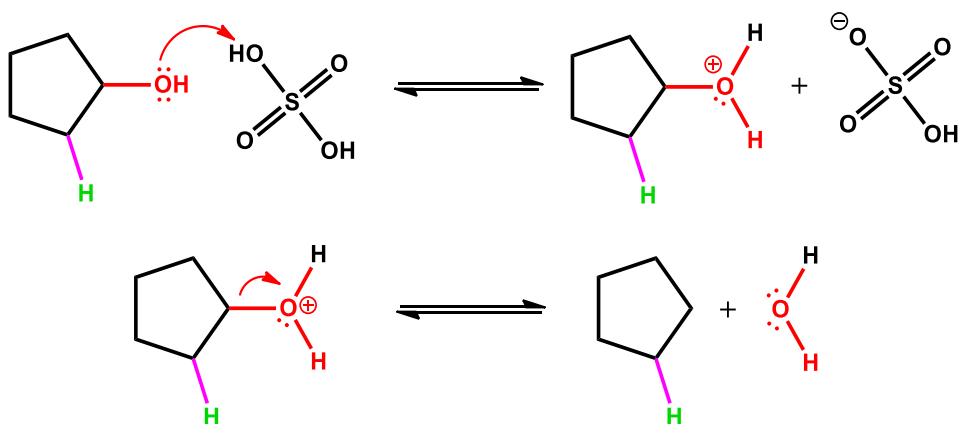
Planar carbocation

Second step

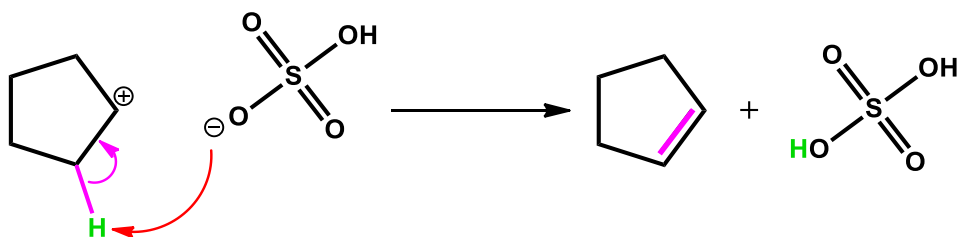
The next step is a fast process whereby a base abstracts a hydrogen proton from a β–carbon atom leading to the formation of a new π bond. Since α and β carbon atoms are connected by a single bond, the free rotation aroundthis bond is possible and therefore two diastereoisomers may form.

Fast process

➲ ***Example***

When cyclopentanol is treated with a strong acid such as sulfuric acid and at high temperature, a dehydration reaction takes place via β–elimination reaction. In this case, the reaction proceeds via E1 mechanism due to the secondary alcohol involved.

$$\text{cyclopentanol (OH)} \xrightarrow[\Delta]{H_2SO_4} \text{cyclopentene} + H_2O$$

Step one

The first step consists in protonating the hydroxy group in order to create a better leaving group, which then gets expelled from the substrate leaving a positive charge on the carbon atom to which it was attached.

Step two

In the next step, the conjugate base of sulfuric acid would abstract a hydrogen proton from a β–carbon atom. This process will lead to the formation of a double bond between the α and β carbon atoms.

Kinetics

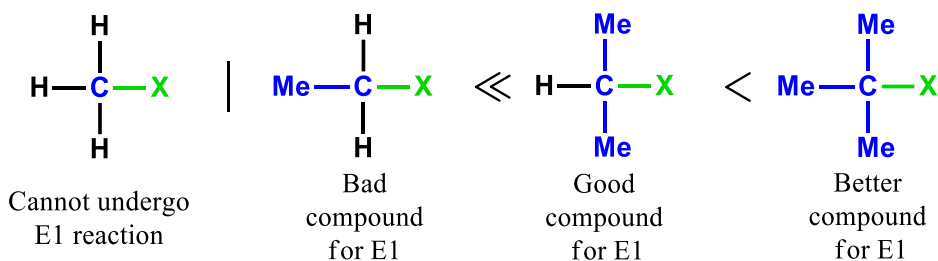
Unimolecular elimination reaction follows the first order kinetics where the reaction rate depends solely on the substrate concentration. In this reaction, the base does not involved in rate-determining step. As a result, increasing or decreasing the concentration of the base will not change the velocity of reaction.

$$\text{Rate} = \text{K}[\text{Substrate}]$$

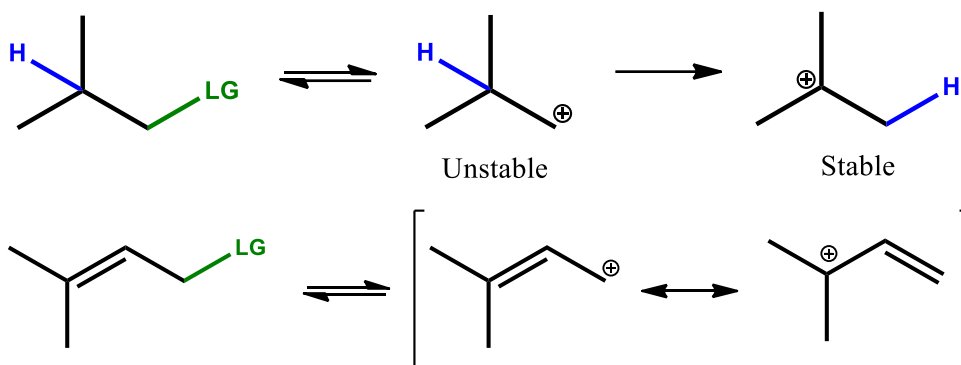
Reaction Conditions

Substrate

Since E1 reaction involves the formation of a carbocation intermediate, tertiary substrates are more favorable for this reaction. In case of a secondary substrate, the base must be weak in order to undergo E1 reaction.

Cannot undergo E1 reaction | Bad compound for E1 ≪ Good compound for E1 < Better compound for E1

In addition, primary substrates do not undergo E1 reaction unless the resulting carbocation can be stabilized by resonance or rearrangement.

Unstable

Stable

Base

E1 reaction goes via first order kinetics law where the rate depends only upon the concentration of the substrate. As a result, with the right substrate, E1 reaction is possible regardless of the strength of the base. Nevertheless, it is important to note that S_N1 reaction can compete with E1 reaction when giving the right conditions. Consequently, it is better to choose a strong base but weak nucleophile, and a bulky base over a small base to avoid S_N1 path.

Solvent

The first step of E1 path requires an ionizing agent that helps in the heterolytic cleavage of the bond connecting the leaving group to the substrate and therefore, polar protic solvents such as water, methanol, and ethanol , which can also participate as bases, do favor E1 reaction.

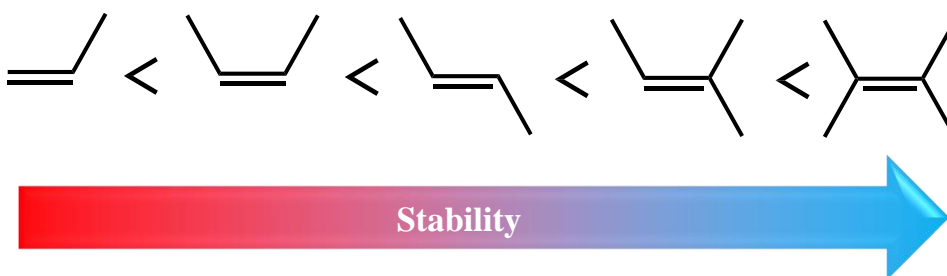
Leaving group

E1 reaction rate is affected by the stability of the nucleofuge. The better the leaving group, the faster the reaction. As a result, substrates that possess a good leaving group such as secondary and tertiary alkyl halides readily undergo β–elimination reaction via E1 mechanism. On the other hand, dehydration of secondary and tertiary alcohols, which proceeds via E1 mechanism, is catalyzed reaction where the hydroxy group is converted into a better leaving group.

III. 2. 2. 1. Regiochemistry and Stereochemistry

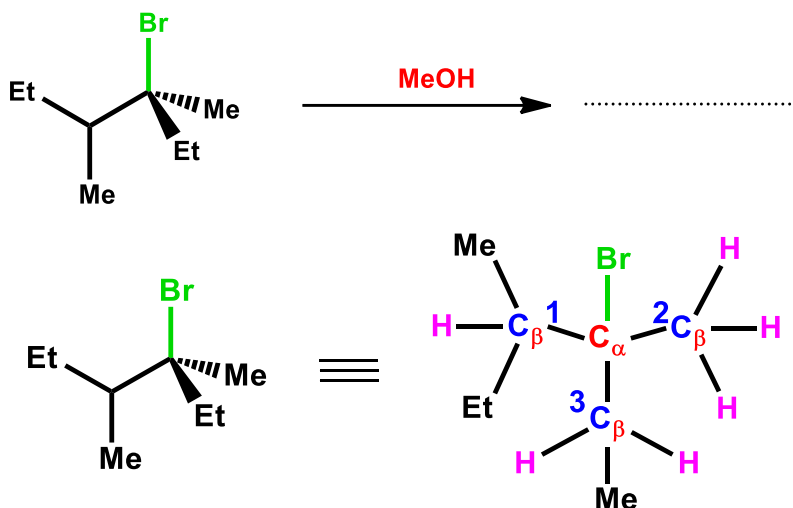
β–elimination reactions are **regioselective** reactions that favor one regio -isomer over the others. The regioselectivity of these reactions depends upon the molecular structure of the substrat e, the steric hindrance of the base used, and from which β–carbon the hydrogen proton is removed. In order to predict which regio-isomer is more likely to form, chemists have established three main rules that focus on the regiochemistry of β–elimination re actions "Zaitsev's rule, Hoffman's rule, and Bredt's rule".

Zaitsev's Rule

Zaitsev's rule states that in β–elimination reactions, the base preferentially abstracts a hydrogen proton from the most substituted β–carbon to give the most substituted alkene (most stable product). This rule is applied when the base involved is not sterically hindered.

➲ ***Example***

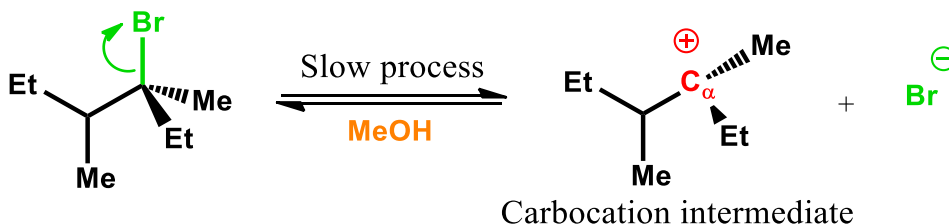
In the following example, a tertiary alkyl bromide is treated with the weak base "methanol", which also acts a polar protic solvent. In this case, there are three available β–carbons from which a hydrogen proton can be abstracted.

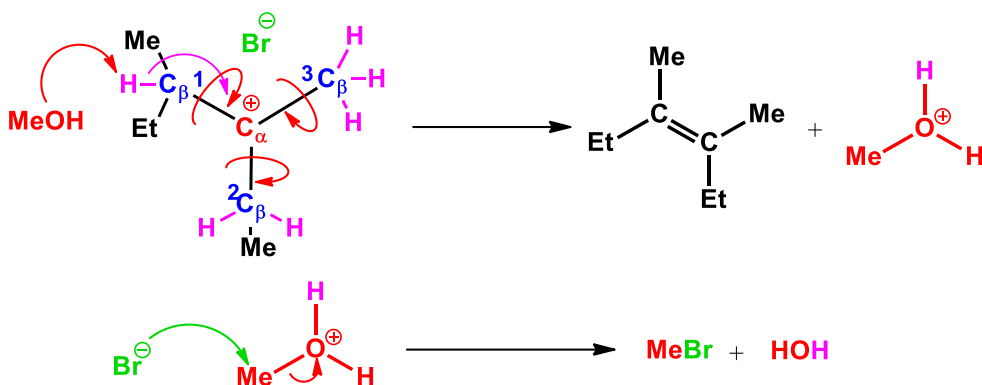
Br
Et Me
Et
Me
MeOH
....

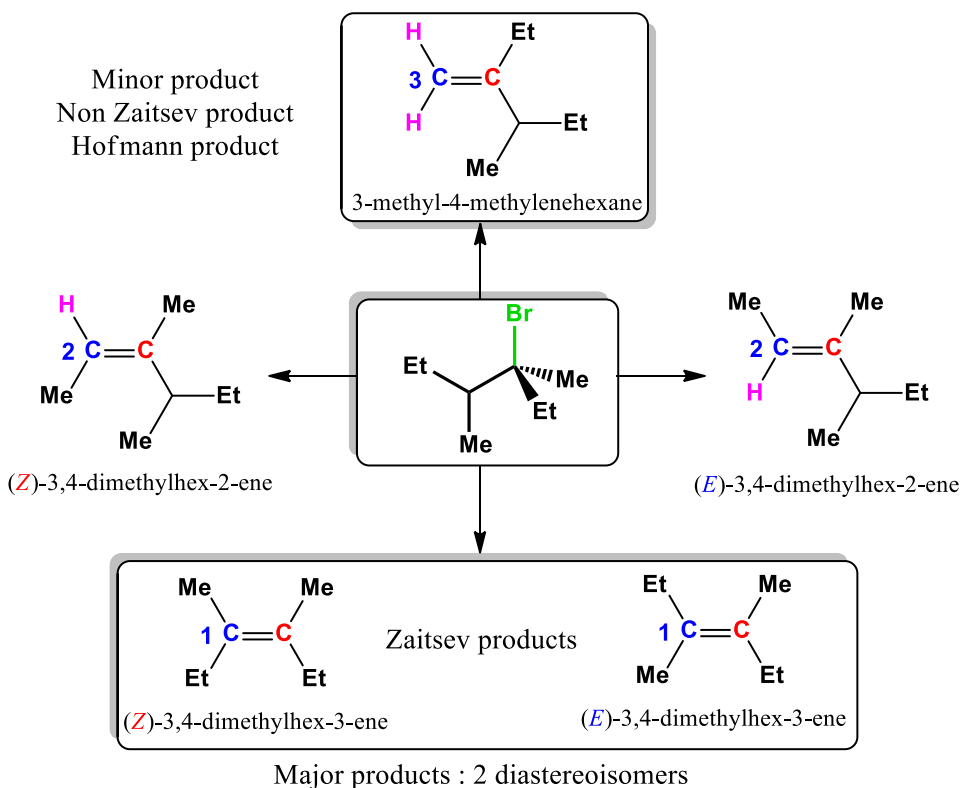
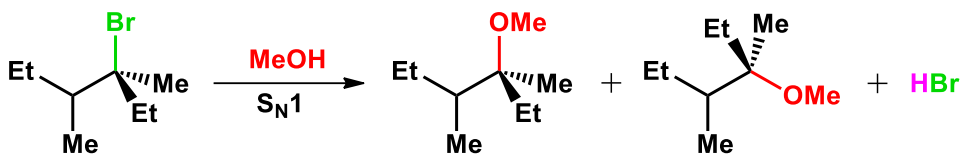
Br
Et Me
Et
Me
≡
Me Br H
H $C_{β}$ 1 $C_{α}$ 2 $C_{β}$ H
Et 3 $C_{β}$ H
H H
Me

Step one

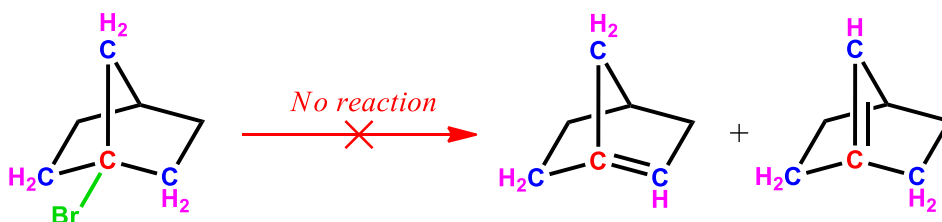
At the beginning, bromine would get expelled from the substrate with the help of the protic polar solvent "methanol" resulting in the formation of a carbocation intermediate. Since the α–carbon is tertiary, the intermediate is stabilized by the inductive donor effect of the three alkyl substituents.

Br
Et Me
Et
Me
Slow process
MeOH
⊕ Me
Et $C_{α}$
Et
Me
+ ⊖ Br

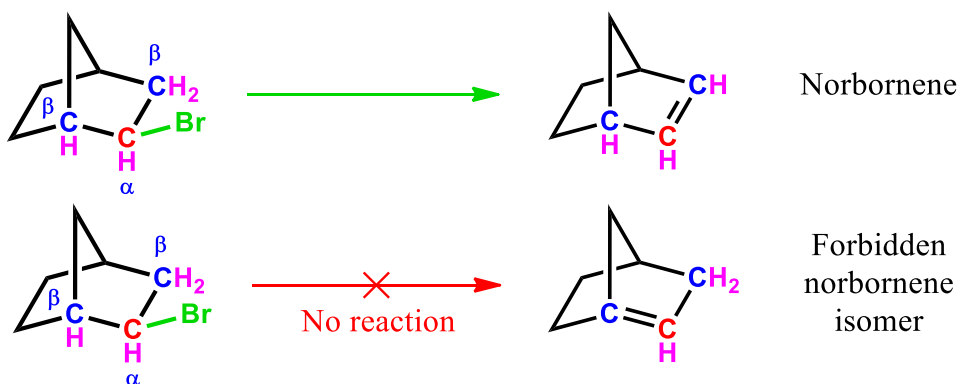
Carbocation intermediate

Step two

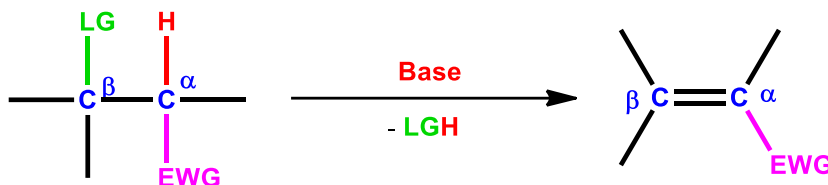
In the second step, the base "MeOH" would abstract a hydrogen proton from a β–carbon atom, which will result in the formation of an alkene. At this point, depending upon from which β–carbon the base abstracts a hydrogen proton, several products with different amounts may form. In this case, because methanol is considerably a small base, Zaitsev's rule can be used to determine the major product(s) and a hydrogen proton is preferentially abstracted from the β–carbon 1.

Moreover, it is important to note that free rotation around σ bond between α and β carbon atoms is possible, which allows the formation of both diastereoisomers "Z and E" and therefore, E1 reaction a **non-stereospecific** reaction. Nevertheless, the steric hindrance in Z diastereoisomer makes it less stable than the E diastereoisomer. As a result, E products would generally prevail over Z diastereoisomers.

Major products : 2 diastereoisomers

Besides the elimination reaction, nucleophilic substitution S_N1 reaction can also occur in this case resulting in a racemic mixture of ethers.

Bredt's Rule

Bredt's rule states that a double bound cannot be placed at the bridgehead carbon atom of a bridged system, unless one ring is sufficiently large for the sp^2 hybridized carbon atom geometry. Consequently, β–elimination reactions cannot occur when the leaving group is attached to the bridgehead atom.

If the leaving group is attached to another carbon atom, the base would abstract exclusively the hydrogen atom attached to a peripheral β carbon atom.

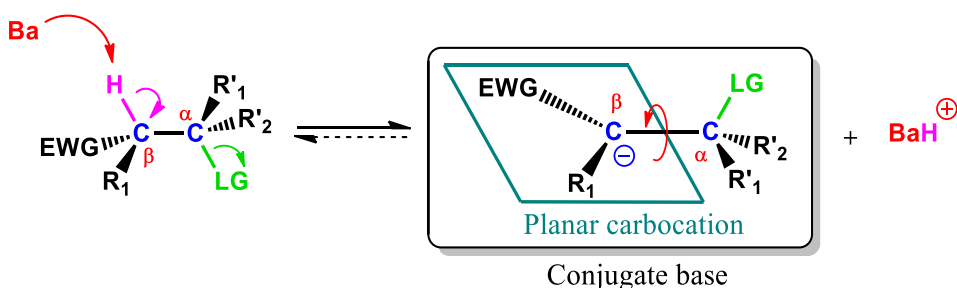
Norbornene

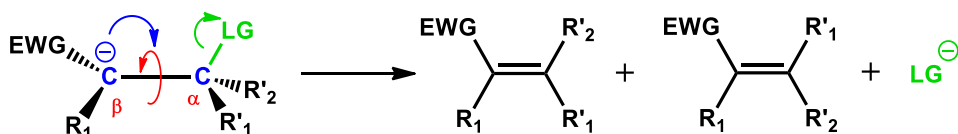
Forbidden norbornene isomer

Unimolecular Elimination Reaction E1cB

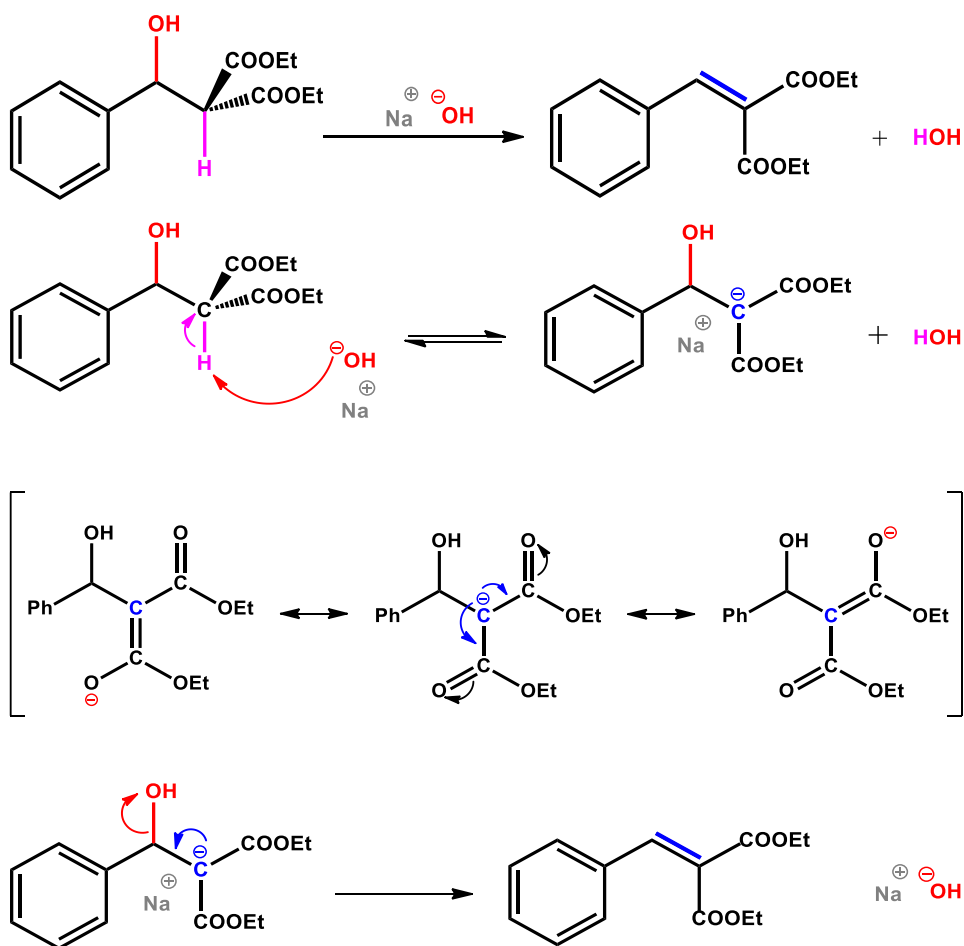
E_1cB (conjugate base) reaction is a unimolecular elimination reaction that occurs under basic conditions with substrates possessing a poor leaving group such as hydroxy group –OH or alkoxy group –OR on β position, an acidic hydrogen, and an electron-withdrawing group such carbonyl or nitro group on α position.

E_1cB reaction proceeds in two steps and passes through the formation of a carbanion intermediate "conjugate base".

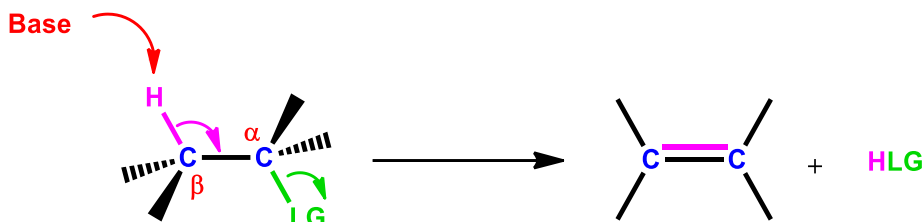
Step one

The first step is a slow process that may or may not be reversible. It is characterized by the deprotonation of the substrate with a moderate to strong base. At this point, the base would abstract the acidic hydrogen proton from the β–carbon atom resulting in a carbanion intermediate, which is also the conjugate base form of the substrate.

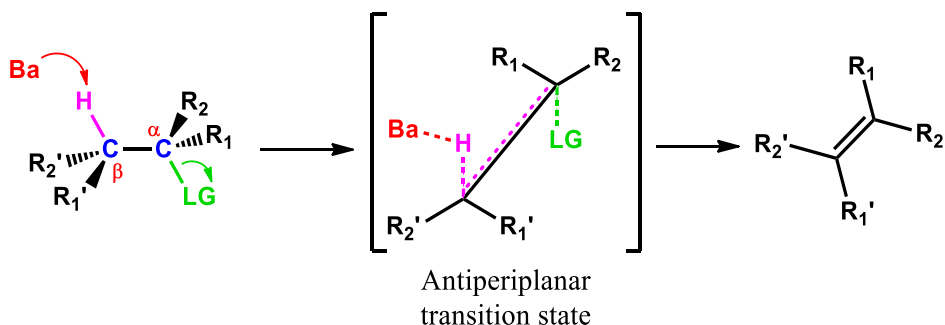
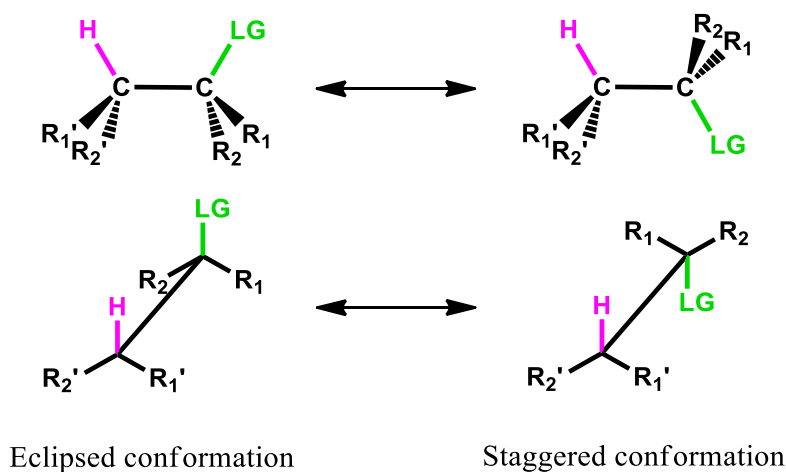
Conjugate base

Second step

The second step is a fast process in which the leaving group departs from the substrate as a new π bond forms between α and β carbon atoms. At this point, the lone pair of electrons left on the carbanion would move towards the neighboring α–carbon atom resulting in the expulsion of this leaving group while a new π bond forms.

➲ ***Example***

A typical example of E1cB reaction is the dehydration step of Knoevenagel condensation reaction. *(Page 241).*

Bimolecular Elimination Reactions E2

E2 reaction is a concerted reaction where both leaving groups leave at the same time. As the base abstracts the hydrogen proton attached to the β carbon atom, the neighboring leaving group gets expelled and a new π bond is formed between α and β carbon atoms.

Moreover, for E2 reaction to occur, the leaving groups must be on the same plane and anti-periplanar to each other. This conformation is necessary for the orbitals to lie in the proper orientation and overlap with each other in order to form the new π bond. As a result, the substrate has to be in the staggered conformation, which has a lower energy than the eclipsed conformation.

Eclipsed conformation Staggered conformation

Antiperiplanar transition state

Kinetics

E2 reaction follows the second order kinetics. In this reaction, the rate is dependent on both of the base and substrate and therefore, increasing the concentration of the base would make the reaction go faster.

$$\text{Rate} = k[\text{Base}][\text{Substrate}]$$

Reaction Conditions

Substrate

E2 reaction can occur with all types of substrates "primary, secondary, and tertiary" as long as they posses a β–hydrogen on anti position with respect to the leaving group.

Base

Because the base is involved in rate -determining step in E2 reaction, the strength and concentration of the base do matter. As a result, E2 reaction proceeds faster with strong concentrated bases such as sodium methoxide, sodium ethoxide, and potassium t-butoxide.

Solvent

Polar aprotic solvents such as DMSO, and DMF are suitable for E2 reaction since they help stabilizing the transition state and do not react with the strong base present in the solution.

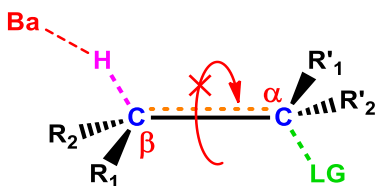
Leaving Group

Just like E1 reactions, E2 reactions occur with substrates that possess a good leaving group. However, if the leaving group is too good, E1 reaction is usually favored.

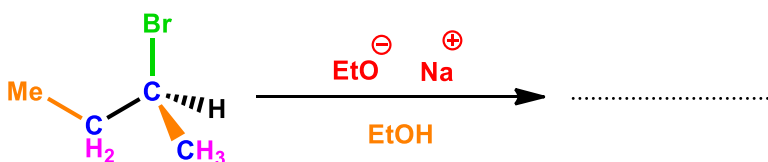
III. 2. 2. 2. Regiochemistry and Stereochemistry

E2 elimination is a **regioselective** reaction that favors certain regio-isomers over the others. However, unlike E1 reaction, E2 reaction is **stereospecific** since it proceeds via a concerted mechanism.

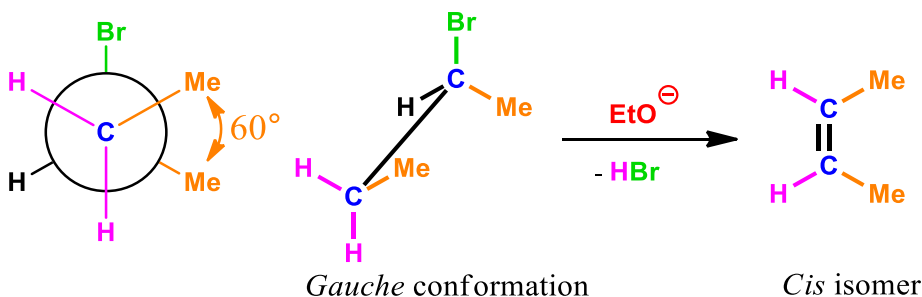
Zaitsev' Rule

With a strong small base, E2 elimination would proceed according to Zaitsev's rule where the most stable products predominate. In this case, the base would preferentially remove the hydrogen proton attached to the most substituted β carbon in order to produce the most substituted alkene. Nevertheless, it is important to note that the free rotation around σ bond between α and β carbons is not allowed at the transition state, which makes the reaction **stereospecific** and also **regiospecific** (*anti*).

Moreover, the staggered conformation where both leaving groups are anti - periplanar to each other can exist in two different forms; *gauche* conformation and *anti*-conformation when the β carbon has two hydrogen atoms. As a result, the substrate would produce two diastereoisomers *cis* and *trans*.

➲ ***Example***

EtO⊖ Na⊕ / EtOH → ....

Depending upon the position of the two methy groups attached to α and β carbons, different diastereoisomers can be obtained as one hydrogen gets removed from the most substituted β carbon. When both methy groups are aligned according to Gauche conformation, E2 elimination would give a *cis* isomer.

60°   EtO⊖   - HBr

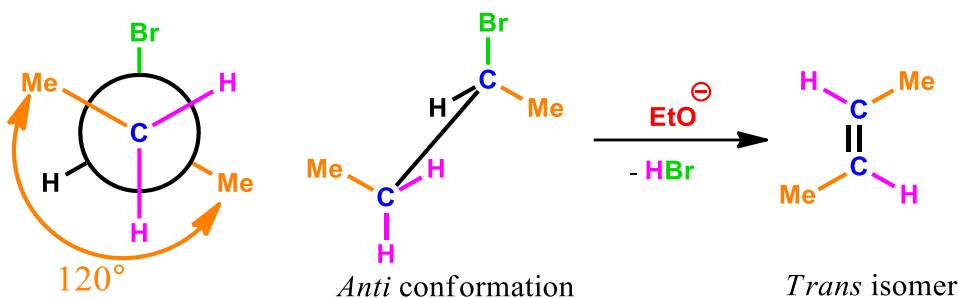
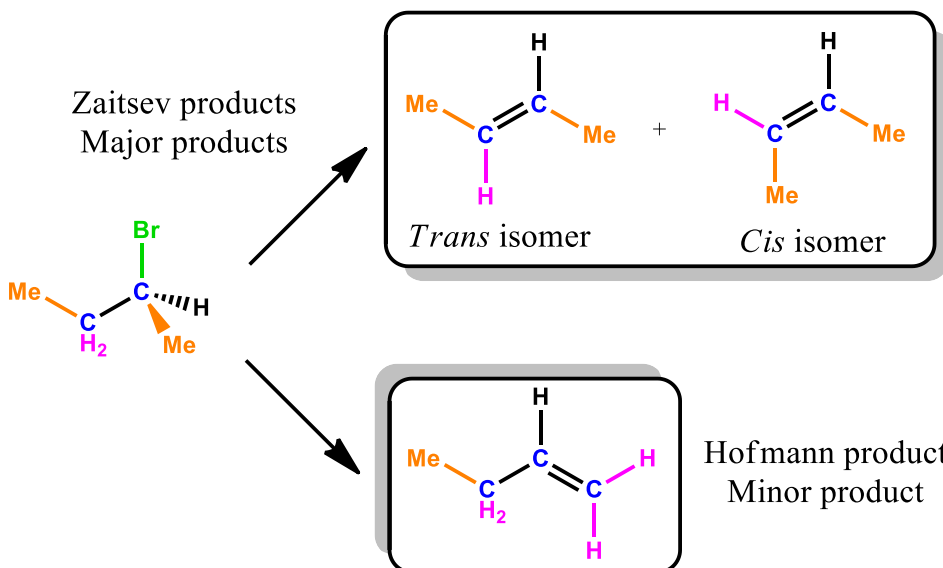
Gauche conformation   *Cis* isomer

On the other hand, when the angle between the two methyl groups is 120°, the *trans* isomer would be produced.

120°

Anti conformation

$EtO^{\ominus}$

- HBr

Trans isomer

In this case, both diastereoisomers are predominant. However, when the hydrogen proton is abstracted from the least substituted β carbon, a small amount of Hofmann product is obtained.

Hofmann's Rule

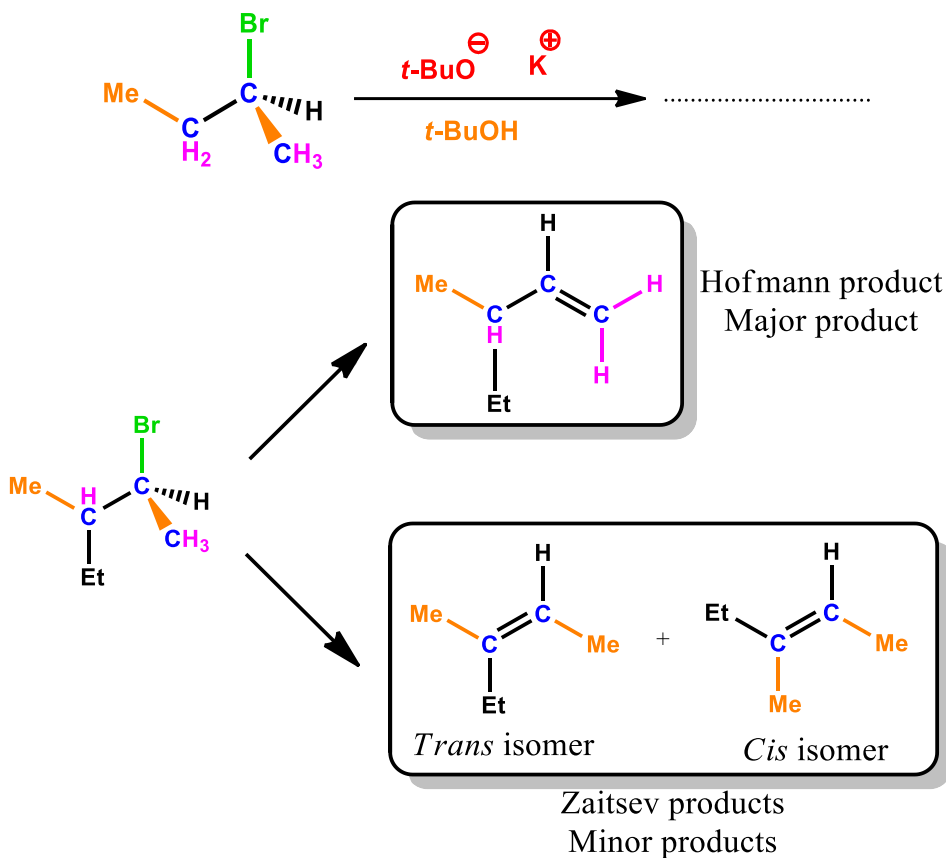
When a β–elimination reaction is carried with a strong bulky base such as potassium t-butoxide, triethylamine, or 2, 6-lutidine, the steric hindrance of the base would impede it from abstracting a hydrogen atom attached to the most substituted β–carbon. However, it would be easier for the base to abstract a hydrogen atom from the least sterically hindered β carbon. Consequently, the major product would be the least substituted compound and it is called the Hofmann Product.

➲ ***Example***

Me–CH_2–C(Br)(H)(CH_3) $\xrightarrow[t\text{-BuOH}]{t\text{-BuO}^{\ominus}\ K^{\oplus}}$ ....

Hofmann product
Major product

Trans isomer + Cis isomer

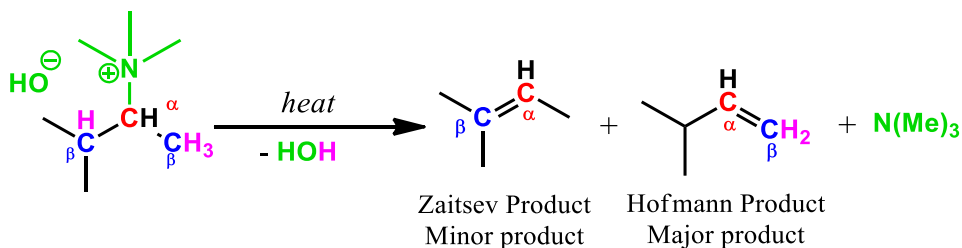
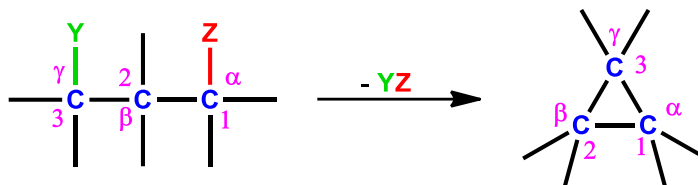
Zaitsev products
Minor products

In a similar way, substrates with bulky leaving groups such as quaternary ammonium or sulfonium salts would preferentially produce more Hofmann products than Zaitsev products.

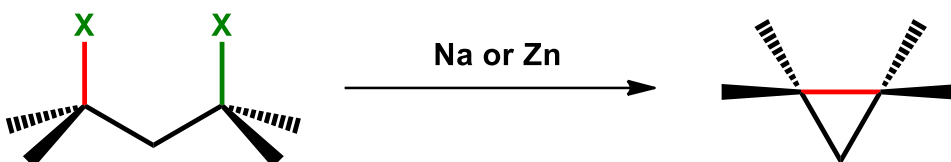
➲ ***Example***

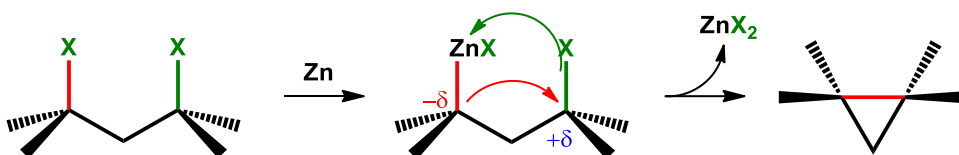
$HO^{\ominus}$ + substrate $\xrightarrow[-\ HOH]{heat}$ Zaitsev product + Hofmann product + $N(Me)_3$

Zaitsev Product
Minor product

Hofmann Product
Major product

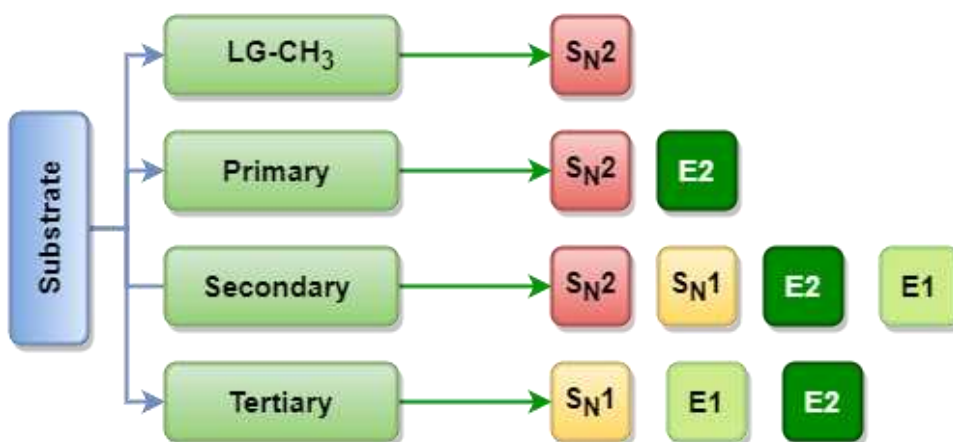
III. 2. 3. γ– Elimination Reactions

1,3-elimination reactions, also called γ-elimination, is the reaction whereby the two leaving groups are on position 1 and 3 to one another. In this case, elimination of these groups leads to the formation of three membered ring compounds.

III. 2. 3. 1. Freund Reaction

Freund reaction is a typical γ-elimination reaction that consists in treating 1,3 - dihaloalkanes with sodium to produce cyclopropanes. This reaction can also take place when treating 1,3-dihaloalkanes with zinc dust in a reaction so called Gustavson reaction

Mechanism

Initially, metal zinc or sodium inserts into the carbon-halogen bond, which leads to the formation of a negative formal charge on this particular carbon atom. later on, this particular carbon would attack the other carbon atom attached to the halogen on position γ resulting in a three membered ring.

III. 3. Competition between SN1, SN2, E1, and E2

Nucleophilic substitution reactions are almost always in competition with elimination reactions. However, it is poss ible to predict which reaction is more likely to take place depending upon reaction conditions and type of substrate. In order to determine which reaction is more favoreable among S_N1, S_N2, E1, and E2, we must take into account mainly three factors; substrate type, reagent stringth, and temperature.

Substrate type

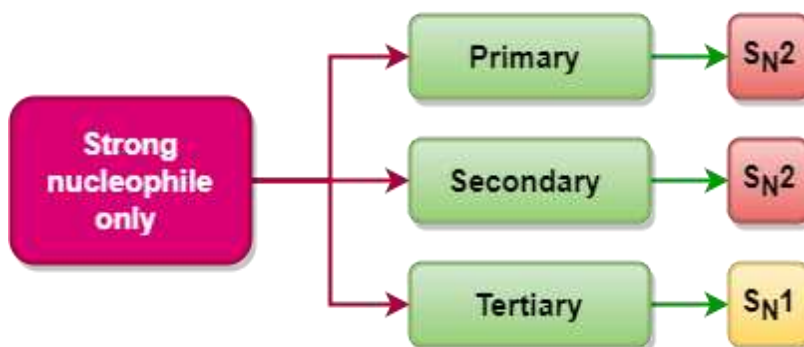
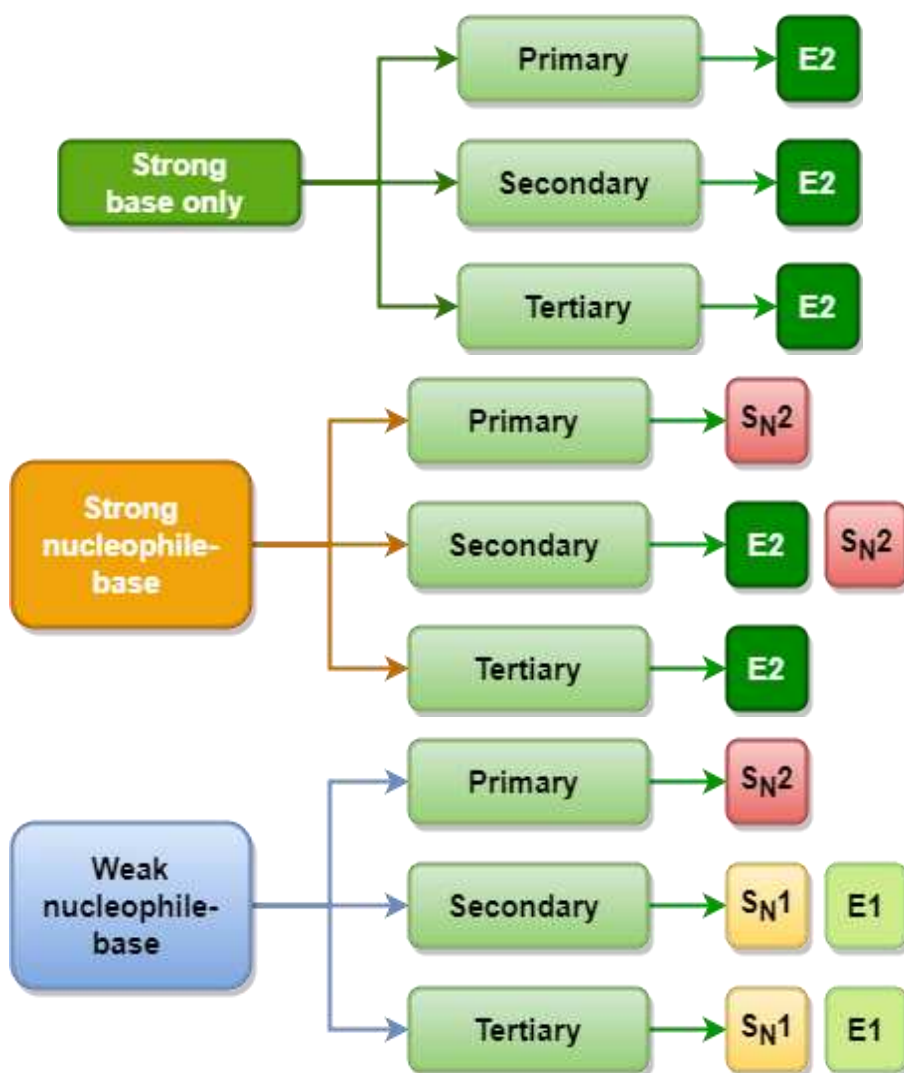
S_N1 and E1 reactions proceed in two steps and involve a carbocation intermediate. As a result, whether these reactions are favorable or not depends upon the stability of the carbocation intermediate that the substrate can form and therefore, S_N1 and E1 reactions are more favorable with tertiary substrates, possible for secondary substrates but never with primary ones " S_N1 is possible with primary allylic and benzylic substrates". On the other hand, S_N2 and E2 reactions are one step reactions where new bonds form at the same time others break. S_N2 reaction is affected by the steric interactions between the substrate and the nucleophile. As a result, it is more favorable with methyl halides, primary and secondary substrates. E2 reaction, on the other hand, is possible regardless of the substrate type as long as there is a β–hydrogen atom *anti*-pariplaner with the leaving group.

Note: *Allylic and benzylic substrates favor first order mechanisms (E1 and SN1).*

Reagent strength

Once we determine which reactions are possible for the given substrate, we must inspect the stringth of the reagent that can be a nucleophile, a base, or a nucleophilic

base. Strong nucleophils and bases favor sec ond order reactions S_N2 and E2 and they are mostly anionic. On the other hand, weak nucleophiles and bases favor first order reactions S_N1 and E1 and they are molecules having lone pairs such as water and ammonia. Moreover, some species can only act as nuc leophiles or bases and they favor S_N2 and E2 reaction.

Bases Only	**Nucleophiles Only**	**Strong Nucleophiles-Bases**	**Weak Nucleophiles-Bases**
H^- ; *t*-BuO^- ; DBN ; DBU ; DIPEA ; LDA	Cl^- ; Br^- ; I^- ; HS^- ; RS^- ; H2S ; RHS	HO^- ; MeO^- ; EtO^-	H_2O ; MeOH ; EtOH ; *t*-BuOH ; NH_3

After we determine to which category the nucleophile/base belong, we can exclude the potential rections we had before according to the follownig diagrams.

Temperature

Temperature plays a significant role when the choice is not clear. If the reaction is carried out at high temperature, elimination reaction is more likely to take place. However, if the reaction is performed at low temperature, substitution reaction is more favorable.

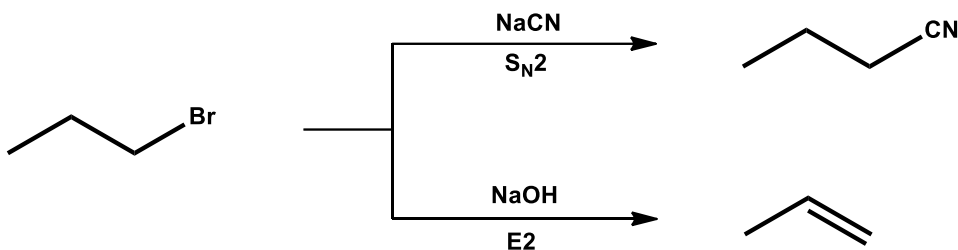
➲ *Examples*

Primary alkyl bromide.

Br

NaCN
S_N2

CN

NaOH
E2

Secondary alkyl bromide.

Br

NaSMe
S_N2

SMe

NaOH ; Δ
E2

EtOH ; Δ
E1

MeOH
S_N1

OMe

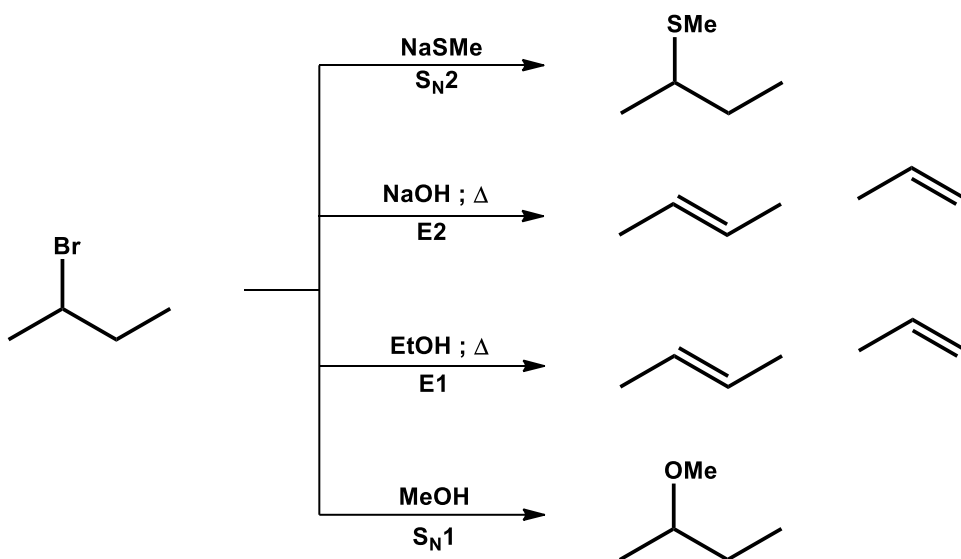
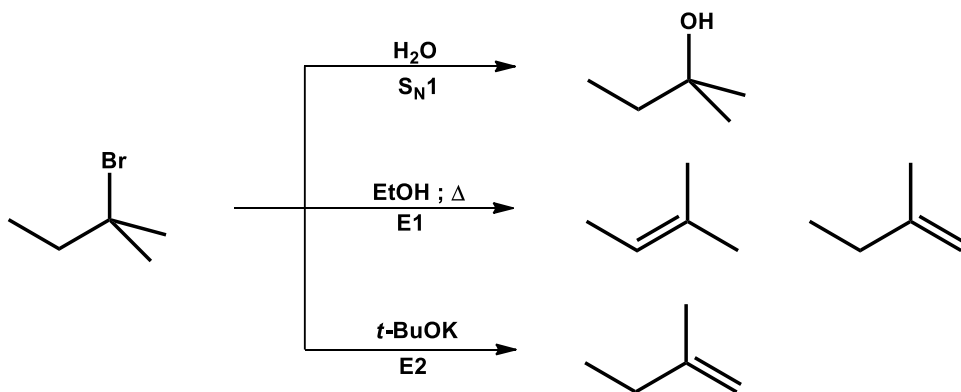
Tertiary alkyl bromide.

Br

H_2O
S_N1

OH

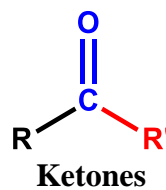
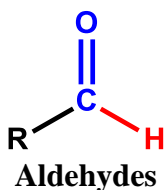
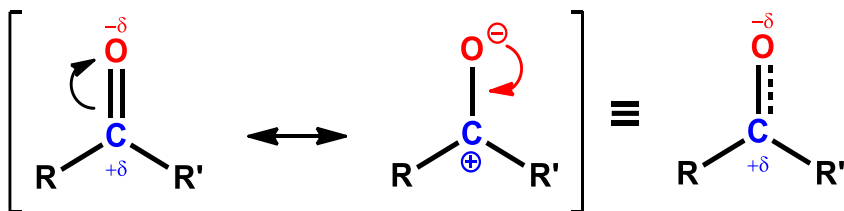
EtOH ; Δ
E1

t-BuOK
E2

III. 4. Addition Reactions

By definition, addition reactions are reactions whereby two species add to two atoms connected with a multiple bond “double or triple bonds” of a substrate. Conceptually, addition reactions follow the opposite pathway of β–elimination reactions and they are categorized into two classes; ionic reactions which involve an ionic intermediate, and non-ionic reactions which do not involve ionic intermediates. Ionic reactions are further subdivided into two types; nucleophilic additions and electrophilic additions. Similarly, non-ionic reactions comprise free-radical additions and concerted additions.

III. 4. 1. Nucleophilic Addition Reactions

III. 4. 1. 1. Nucleophilic Addition Reactions to Aldehydes and Ketones

Aldehydes and ketones are organic compounds that possess a carbonyl group attached to a hydrogen atom in case of aldehyde, an alkyl or aryl group in case of ketones. The main reaction of these compounds in nucleophilic addition whereby a nucleophile adds to the carbonyl carbon atom while the oxygen receives a hydrogen proton.

Since oxygen is more electronegative than carbon atom, it pulls the electron of the carbonyl double bonds towards its nucleus. As a result, a partial negative charge forms on the oxygen atom while a partial positive charge forms on carbonyl carbon. This particular property makes aldehyde and ketones suitable for nucleophilic addition reaction.

Reactivity of Aldehydes and Ketones

In term of reactivity towards nucleophiles, aldehydes are more reactive than ketones due to the steric strain in ketones, which mak es the electrophilic site less accessible.

On the other hand, ketones tends to be more stable than aldehydes since the carbonyl group in ketones is attached to two electron -releasing groups that can be alkyls +*I* or aryls +*M*.

General Mechanism

Nucleophile addition to aldehydes and ketones can be carries out with acid or base catalyst and it proceeds in two steps.

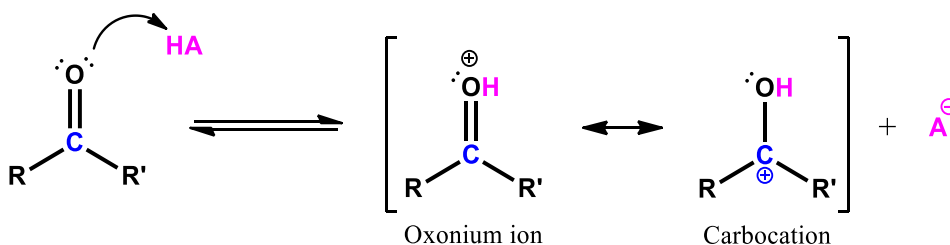
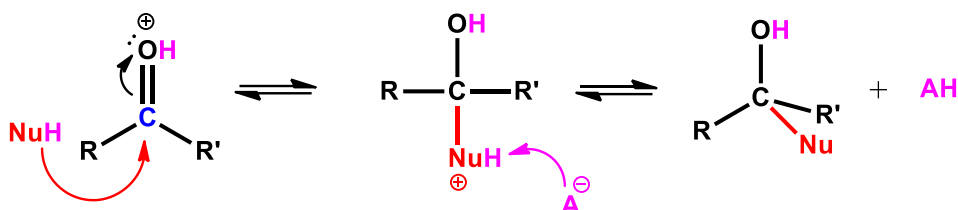
Acid Catalyzed Reactions

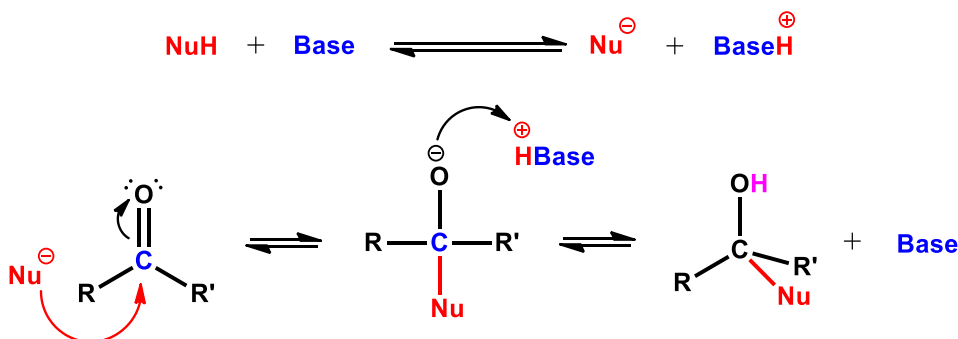
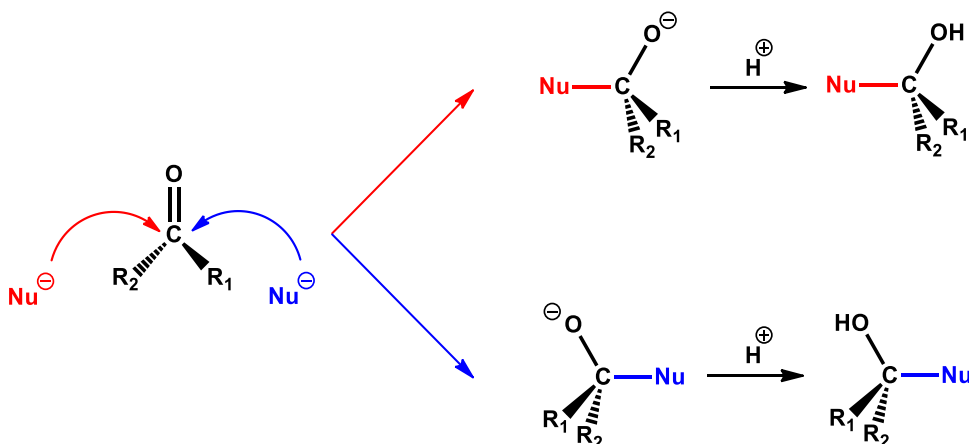
Under acidic conditions, the first step consists in protonating the carbonyl oxygen, which gives rise to a more electrophilic carbonyl carbon.

HA

Oxonium ion

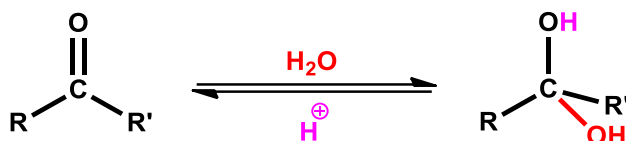
Carbocation

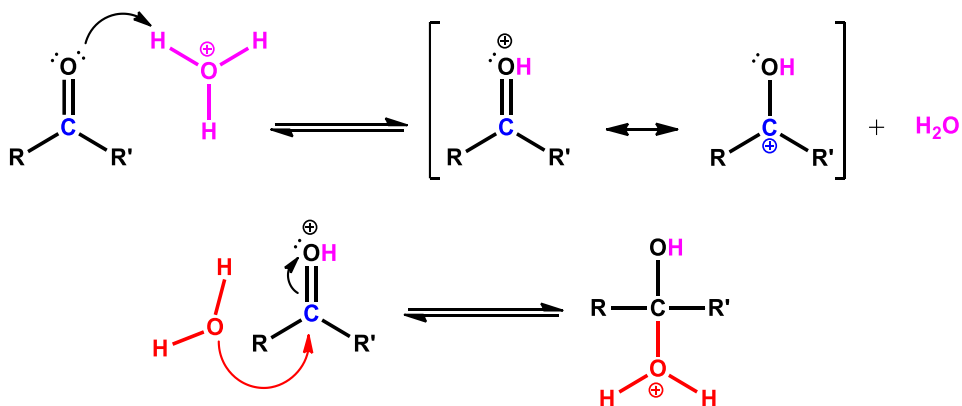
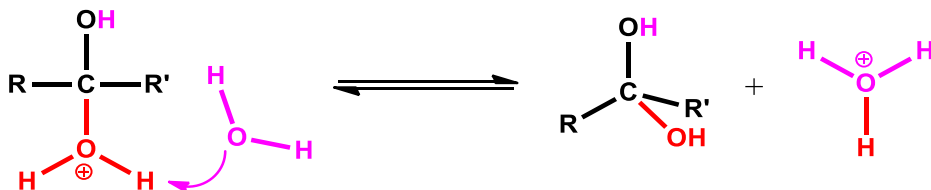
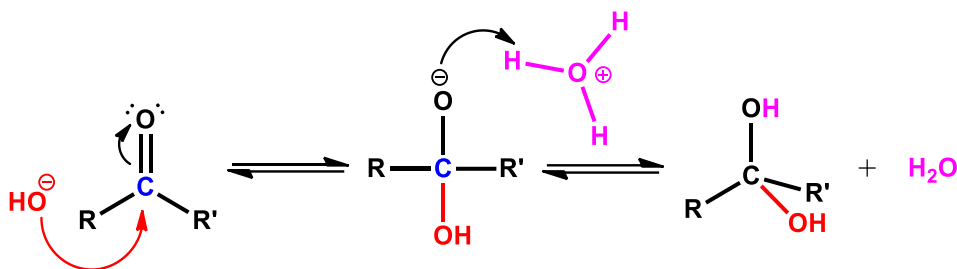
+ $A^{\ominus}$

In the next step, the nucleophile adds to the carbonyl carbon atom resulting in an ionic tetrahedral intermediate, which then gets dep rotonated to form a hydroxy group.

Base Catalyzed Reactions

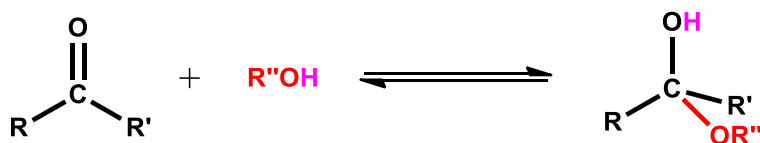
When performing a nucleophilic addition reaction under basic conditions, the nucleophile first reacts with the base in order to generate a stronger nucleoph ile, which then add to the carbonyl carbon resulting in an ionic tetrahedral intermediate. The next step involves protonation of the ionic intermediate, which can be accomplished by either a protic solvent or the conjugate acid of the base catalyst.

Carbonyl carbon is an sp^2 hybridized carbon that has a planar geometry. As a result, at the course of a nucleophilic addition, the nucleophile can adds from either sides of the carbonyl carbon resulting in a mixture of two ster eoisomer, which makes nucleophilic addition a **non-stereoselective** reaction.

Common Reactions of Aldehydes and Ketones

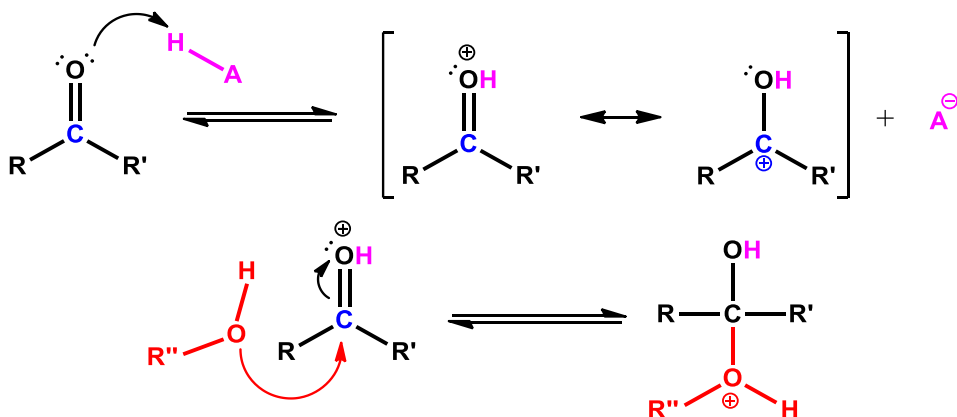
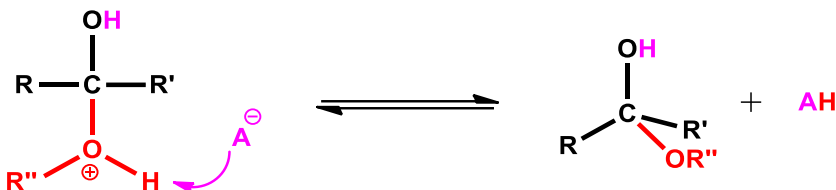
Nucleophilic addition to aldehydes and ketones is a fundamental reaction in organic chemistry since it transforms carbonyl function into other reactive functional groups.

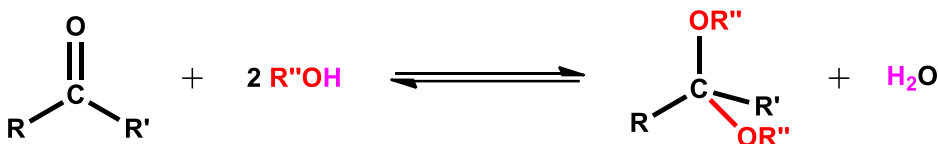
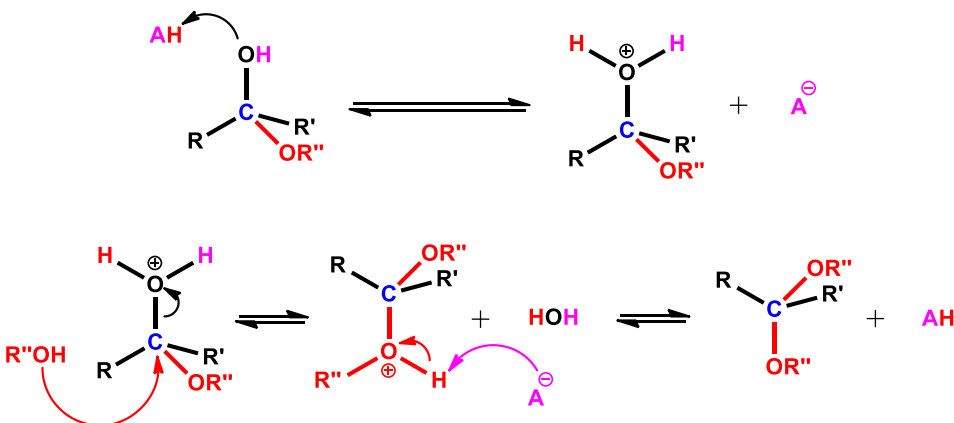
Formation of Hydrates

Hydration of aldehydes and ketones is a reversible reaction that consists in adding a water molecule to the carbonyl group, which gives germinal diols.

Because water is a weak nucleophile, this reaction must be catalyzed with an acid or base catalyst and it proceeds in two reversible steps.

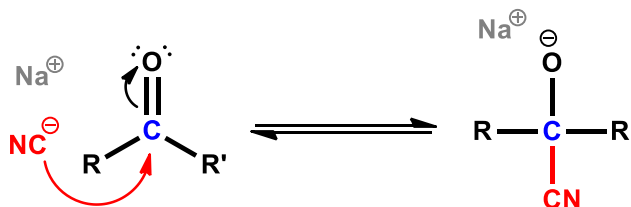
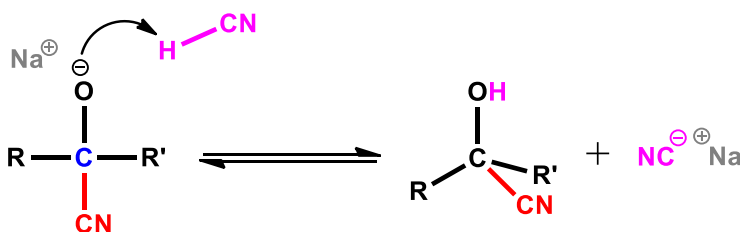
Under acidic aqueous condition, the oxygen atom of carbonyl gets protonated resulting in an activated carbonyl carbon. At this point, a water molecule can easily add to the carbonyl carbon resulting in an ionic tetrahedral intermediate.

In the next step, a nearby basic species such as water, would abstract a hydrogen proton from the protonated hydroxy group and leads to the formation of a germinal diol.

Base catalyzed hydration proceeds in a different way. Initially, the strong nucleophile HO^- adds to the carbonyl carbon resulting in a tetrahedral anionic intermediate, which then gets protonated to give the corresponding a germinal diol.

Formation of Hemiacetals, Hemiketals, Acetals, and Ketals

Formation of hemiacetals and hemiketals occurs when one equivalent of an aldehyde or ketone reacts with one equivalent of an alcohol. Since the nucleophile involved is not sufficiently strong to attack the carbonyl carbon, these reactions are carried out under acidic or basic conditions. However, acid catalyzed reactions tend to be more efficient and fast.

R' = H: aldehyde, hemiacetal
R' = Alkyl or aryl: Ketone, hemiketal

Initially, the oxygen atom of the carbonyl abstracts a hydrogen proton from the acid catalyst resulting in an activated carbonyl carbon. Later on, a nucleophilic attack would take place. At this point, the alcohol would add to the carbonyl carbon forming, this way, an ionic tetrahedral intermediate.

Finally, the conjugate base of the acid catalyst would deprotonate the ionic tetrahedral intermediate, which leads to the final product, hemiacetal for aldehyde, or hemiketal for ketone.

Furthermore, it is important to know that all these reactions are reversible. Nevertheless, for aldehydes, the equilibrium tends to shift towards the hemiacetal. On the other hand, because hemiketals are more reactive than ketones, the equilibrium tends to shift towards ketones instead of hemiketals.

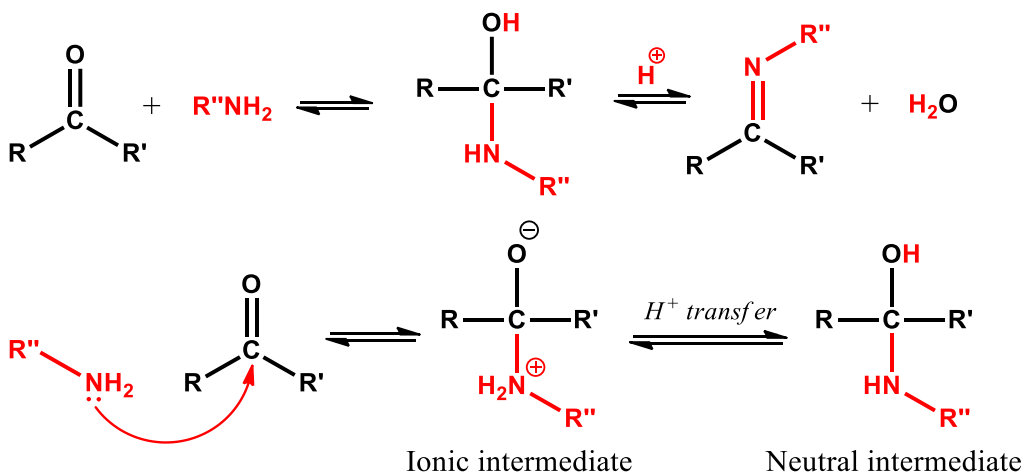
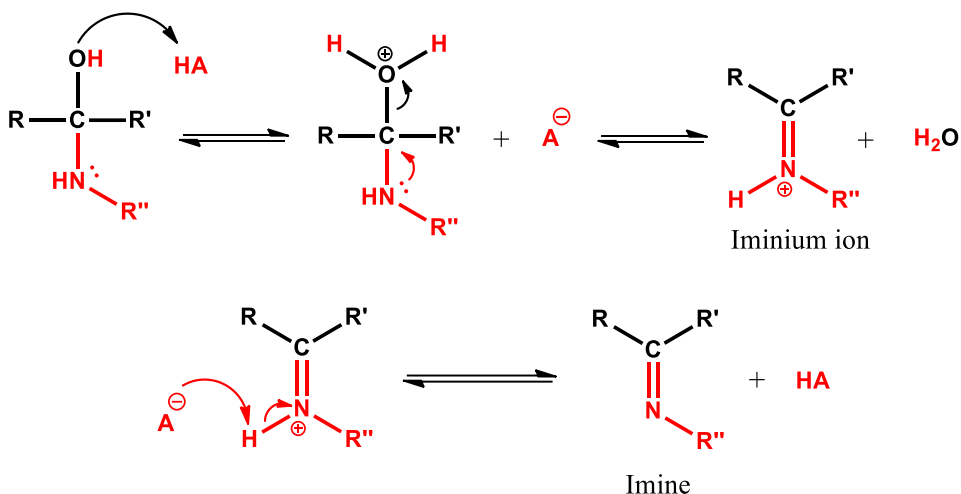
If one equivalent of an aldehyde or ketone reacts with two equivalents of an alcohol, the reaction does not stop and the hemiacetal or hemiketal undergoes a nucleophilic substitution in which hydroxy groups get displaced by an alkoxy group. In this case, aldehydes would produce acetals while ketones would give ketals.

R' = H: aldehyde, acetal
R' = Alkyl or aryl: Ketone, ketal

Formation of Cyanohydrins

Cyanohydrin synthesis is accomplished by treating an aldehyde or ketone with cyano ions in a buffered solution. This reaction proceeds via nucleophilic addition in two reversible steps and follows the first order kinetics.

The first step of cyanohydrin formation is characterized by nucleophilic addition of the cyano ion to the carbonyl carbon atom. In this case, cyano ions are sufficiently nucleophilic to attack the partially positive carbonyl carbon atom resulting in an ionic tetrahedral intermediate.

The second step consists in protonating the alkoxy group, which leads to the formation of the corresponding cyanohydrin.

Formation of Imines and Enamines

Aldehydes and ketones react with primary amines to produce imines. This reaction proceeds in two reversible steps; initially, and often without catalyst, the primary amine attacks the carbonyl carbon resulting in an ionic tetrahedral intermediate, which eventually transforms into a neutral one after a hydrogen transfer.

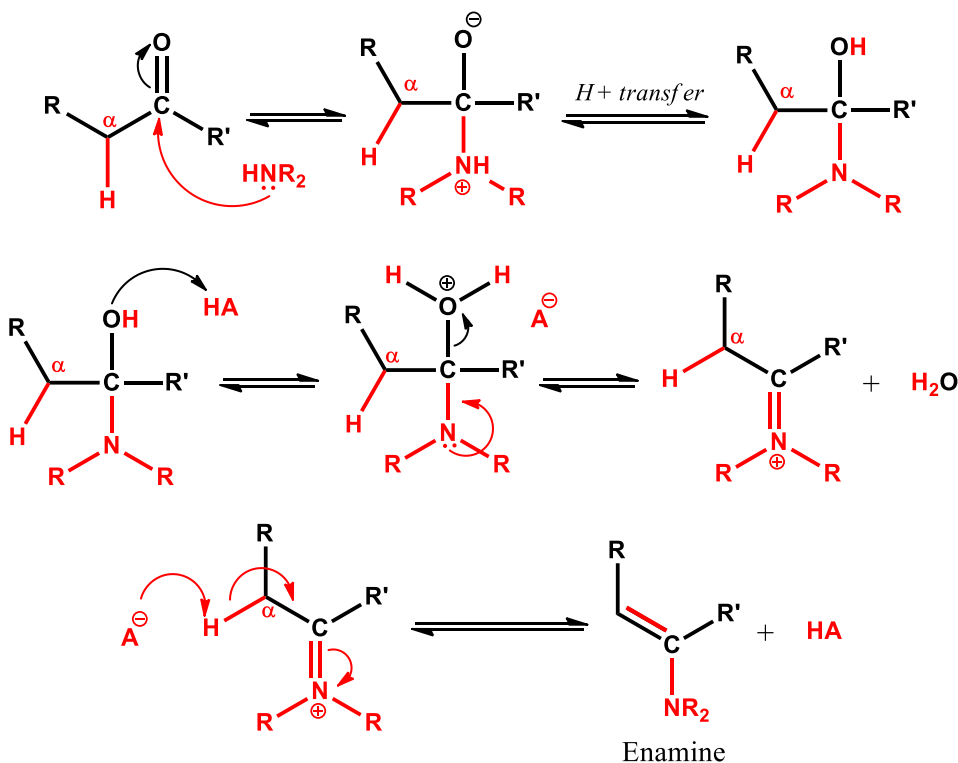
H^+ transfer

Ionic intermediate Neutral intermediate

The next step consists in dehydrating the neutral intermediate under acidic condition leading to the final product “imine”.

Iminium ion

Imine

When secondary amines react with aldehydes or ketones, the reaction proceeds in similar way. However, since the iminium ion has no available hydrogen atom attached to the nitrogen, which is supposed to be abstracted in the second step, the reaction proceeds in different way. In this case, if there is an available hydrogen on the α carbon atom, it can be removed leading to the formation of an enamine.

H+ transfer

Enamine

III. 4. 2. Electrophilic Addition Reactions

Electrophilic addition reactions are the most characteristic reaction of alkenes and alkynes. These reactions involve electrophiles and pass through the formation of ionic intermediates. Moreover, electrophilic addition reaction are so important in organic chemistry synthesis since they interconvert alkenes and alkynes into other important functional groups.

III. 4. 2. 1. General mechanisms

Depending upon the type of electrophile used, electrophilic reactions differ from one another. However, they all proceed in two steps and pass through the formation of an ionic intermediate. The first step is a slow process in which the electrophile adds to an sp^2 or sp carbon atom resulting in an ionic intermediate. The next step is a fast process where a nucleophilic species adds to the neighboring sp^2 or sp carbon atom.

III. 4. 2. 2. Regeochemistry and Stereochemistry

Electrophilic addition reactions have different properties regarding regiochemistry and stereochemistry. In general, reactions that involves asymmetrical reagents are regioselective that follow Markovnikov's rule.

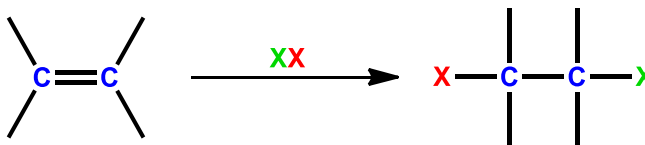
Markovnikov's rule

Markovnikov's rule is used to study the regiochemistry of electrophilic reactions. It helps in predicting which adduct would prevail over the others. According to Markovnikov's rule, electrophiles preferentially add to the most hydrogenated carbon atom to produce the most stable ionic intermediate and product.

III. 4. 2. 3. Dihalogenation Reaction

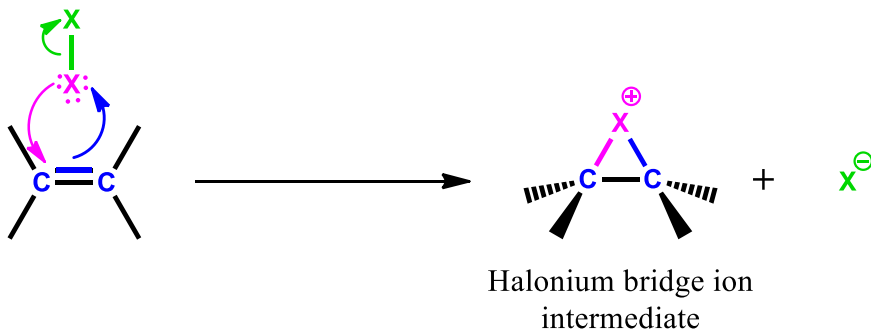
Dihalogenation is an electrophilic addition reaction where two identical halogens XX add to a substrate across the multiple bond. This reaction can occur in both alkenes and alkynes.

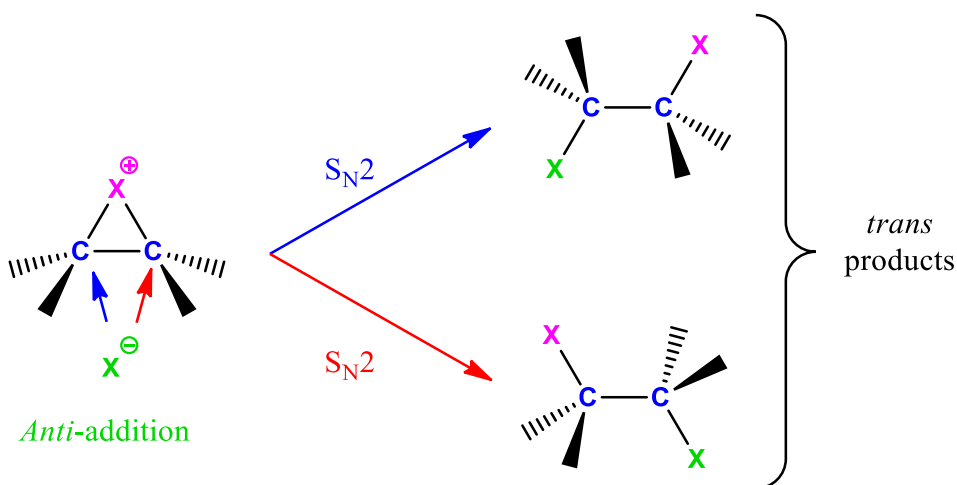
Alkenes

Alkenes react with dihalogens to produce vicinal alkyl halides. In this case, the π bond breaks and each sp^2 carbon atom binds to a halogen atom.

Mechanism

Addition of identical halogens to an alkenes proceeds in two steps and involves an ionic intermediate.

Step one

Initially, the electrophilic halogen adds to the π bond resulting in a cyclic ionic intermediate known as halonium bridge ion and a halide ion.

Step two

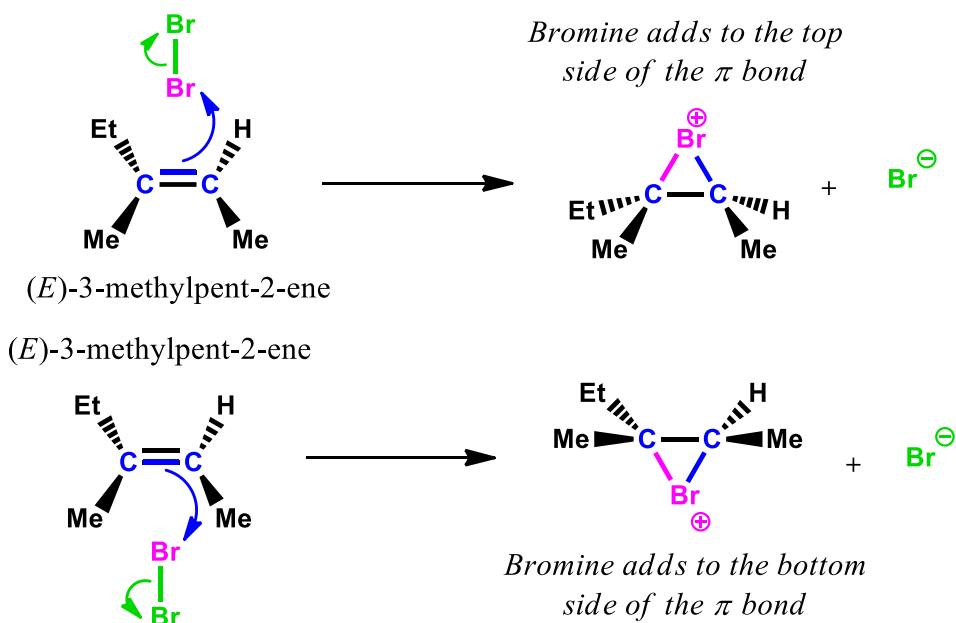
In the next step, the nucleophilic halide ion would attack one of the carbon atoms of the cyclic intermediate, which leads to opening the cycle and forming vicinal alkyl halide. This step is analogous to S_N2 reaction and the nucleophilic attack can only occur via *anti*-addition.

Regiochemistry and Stereochemistry

Dihalogenation reaction consists in the addition of a symmetrical dihalogen molecule to an unsaturated substrate. Since both halogens are identical, Markovnikov's rule would not be relevant and therefore dihalogenation addition is a **non-regioselective** reaction. Nevertheless, this reaction is **regiospecific** because nucleophilic attack can only occur from the backside of the bridge ion intermediate "anti-addition".

➲ ***Example***

Dibromination of (*E*)-3-methylpent-2-ene will give a vicinal dibromoalkane. The reaction goes in two separated steps and involves a bromonium ion bridge.

First step

At first, the substrate approaches dibromine molecule ionizing the bond connecting the two bromine atoms together, which eventually leads to the formation of bromonium ion intermediate. At this point, the other bromine atom would acquire full negative charge. Moreover, the electrophilic bromine can add to the π bond from either sides.

Second step

Once the intermediate forms, the other bromide ion would act as a nucleophile and attack any carbon atom connected to the bromonium ion. This nucleophilic attack proceeds exclusively via an *anti*-addition where both halogen are on the same plane but each one points in the opposite direction with a precise 180°.

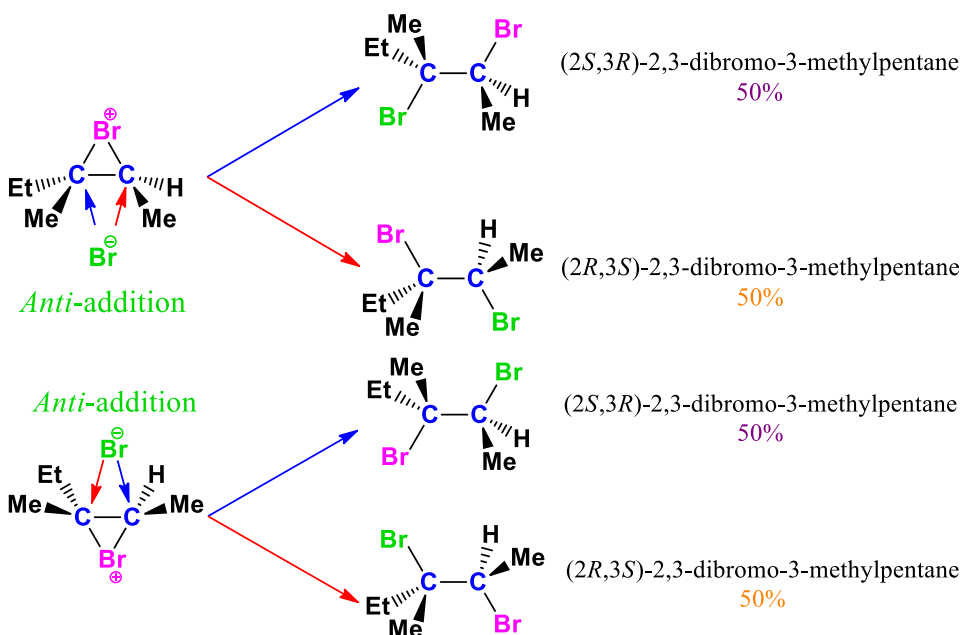
(2*S*,3*R*)-2,3-dibromo-3-methylpentane
50%

Anti-addition

(2*R*,3*S*)-2,3-dibromo-3-methylpentane
50%

Anti-addition

(2*S*,3*R*)-2,3-dibromo-3-methylpentane
50%

(2*R*,3*S*)-2,3-dibromo-3-methylpentane
50%

The second step would therefore produce a mixture of two stereoisomers, which makes dihalogenation addition is a **non-stereoselective reaction**. In addition, although dihalogenation proceeds via *anti*-addition, the reaction outcome would not differ whether the electrophilic bromine adds to the top side or the bottom side due to the symmetry of the dihalogen involved.

In case of (*Z*)-3-methylpent-2-ene, different products would be obtained than the ones produced when using (*E*)-3-methylpent-2-ene and therefore, dihalogenation is a **stereospecific reaction** where specific stereoisomer reagent would give specific stereoisomer products.

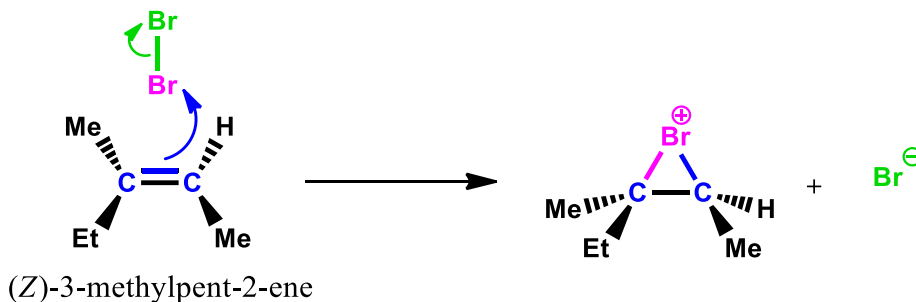
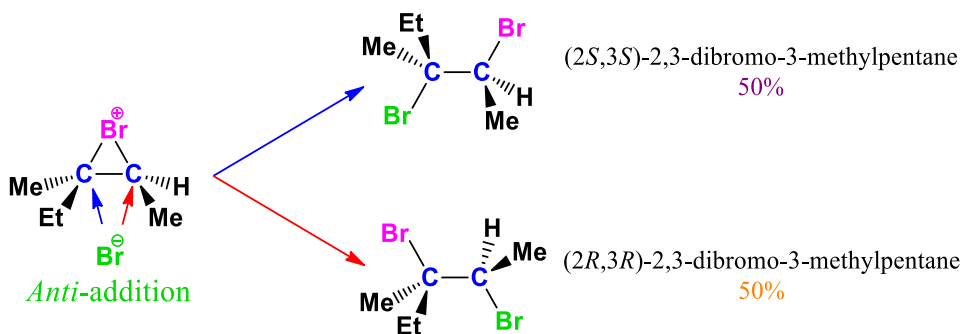
Step one

(*Z*)-3-methylpent-2-ene

Second step

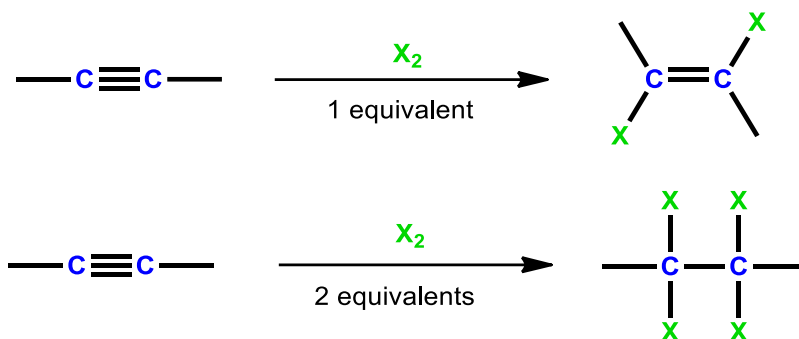
(2*S*,3*S*)-2,3-dibromo-3-methylpentane
50%

(2*R*,3*R*)-2,3-dibromo-3-methylpentane
50%

Anti-addition

Alkynes

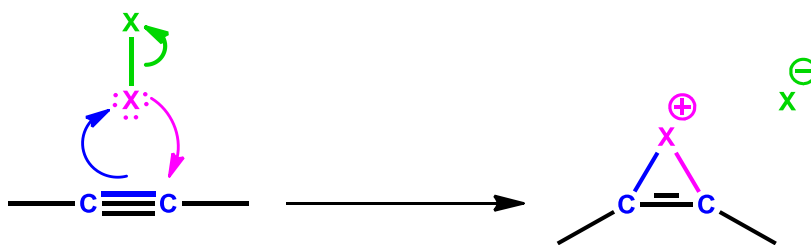
Unlike alkenes, alkynes have two π bonds, which makes them susceptible for further electrophilic addition. As a result, dihalogenation of alkynes can yield either a dihalogenated alkene or an alkyl tetrahalide depending upon reaction condition. Alkynes react with one equivalent of a dihalogen to give trans-dihalogenated alkenes. However, when two equivalents of dihalogen react with one equivalent of alkynes, alkyl tetrahalide are obtained.

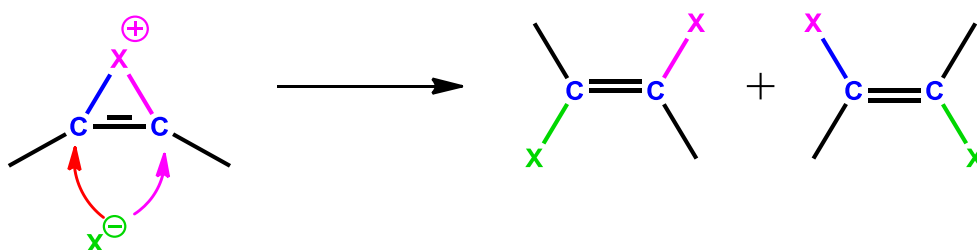
X_2
1 equivalent

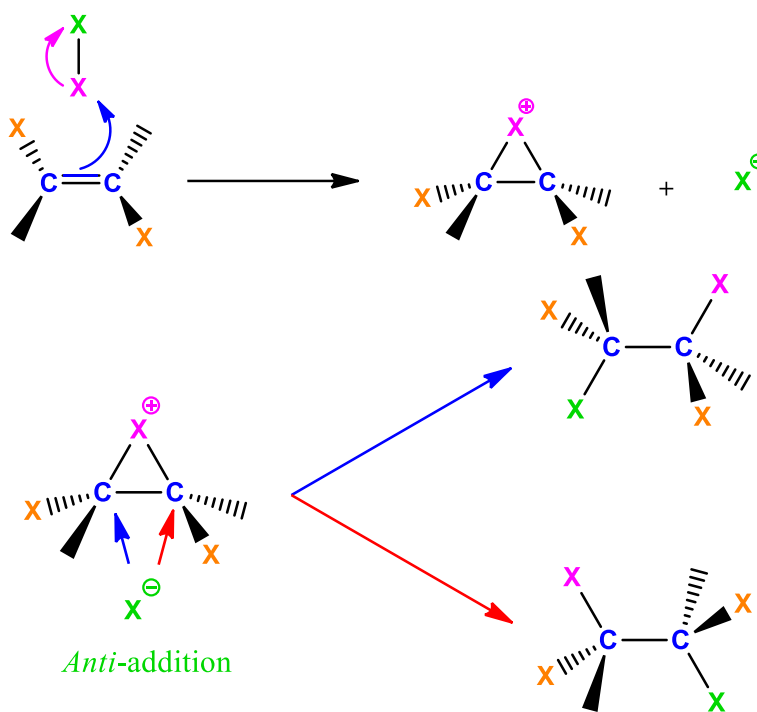
X_2
2 equivalents

Mechanism

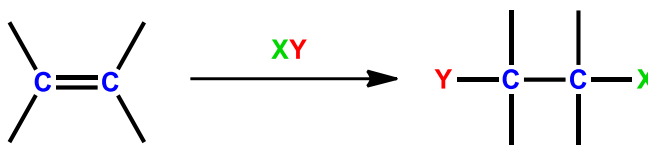
The mechanism of alkynes halogenation is similar to that of alkenes. It proceeds in two steps and involves a halonium bridge ion intermediate.

Step one

Addition of the electrophile and formation of cyclic ionic intermediate.

Step two

The next step is characterized bythe *anti*-addition of the nucleophilic halide, which leads to *trans*-dihalide alkene.

If the reaction is performed with two molecular equivalents of the dihalide, further dihalogenation would take place resulting in an alkyl tetrahalide is formed.

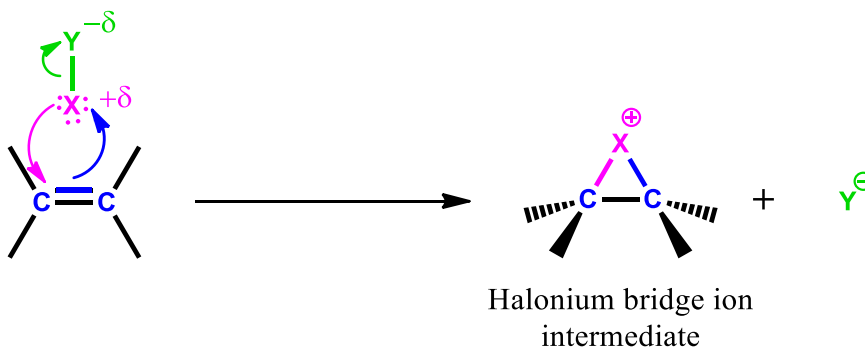
Anti-addition

III. 4. 2. 4. Halogenation Reaction

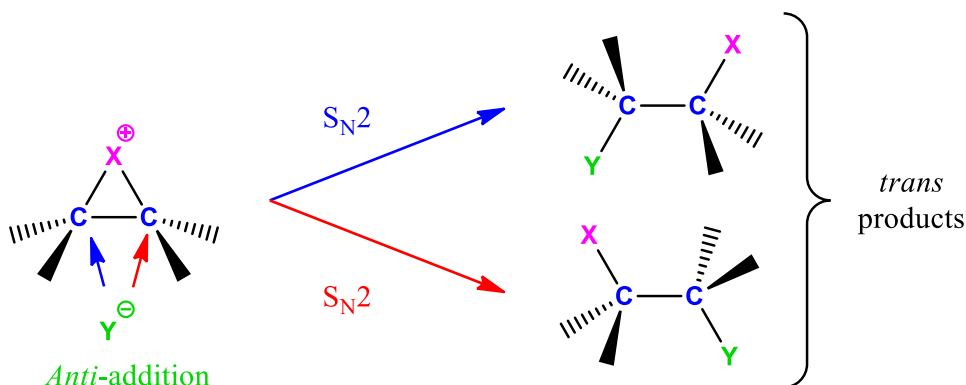
Halogenation of alkenes is an electrophilic addition where two different halogens XY add to a substrate across the multiple bond.

Mechanism

Halogenation of alkenes follows the same mechanism of dihalogenation. It proceeds in two separated steps and involves a halonium ion intermediate to produce a vicinal dihalide alkanes.

Step one

Since the dihalogen molecule is asymmetrical, the more electronegative atom would pull the bonding elections towards its nucleus, which create a dipole-dipole moment with an electron deficient side. In this case, the least electronegative halogen will act as an electrophile.

Halonium bridge ion intermediate

Second step

The second step involves the *anti*-addition of the nucleophilic halide to either carbon atoms attached to the halonium ion.

Regiochemistry and Stereochemistry

Halogenation reaction is a **regioselective reaction** that does respect Markovnikov's rule where the major products is the one obtained when the least electronegative halogen "electrophile" adds to the most hydrogenated carbon atom. On the other hand, the most electronegative halogen adds to the least hydrogenated carbon atom. Furthermore, halogenation of alkenes is a **regiospecific reaction** that proceeds exclusively via *anti*-addition.

➲ ***Example***

Bromochlorination of (*E*)-3-methylpent-2-ene will give a saturated hydrocarbon with a bromine and chlorine attached to vicinal carbon atoms.

Step one

Since chlorine has a higher electronegativity than bromine, it would withdraw the bonding electrons towards it nucleus resulting in a partial positive charge on the bromine. As a result, bromine will act as an electrophile and add to the π bond to form a bromonium ion bridge.

Cl
Br
Et
H
C
C
Me
Me

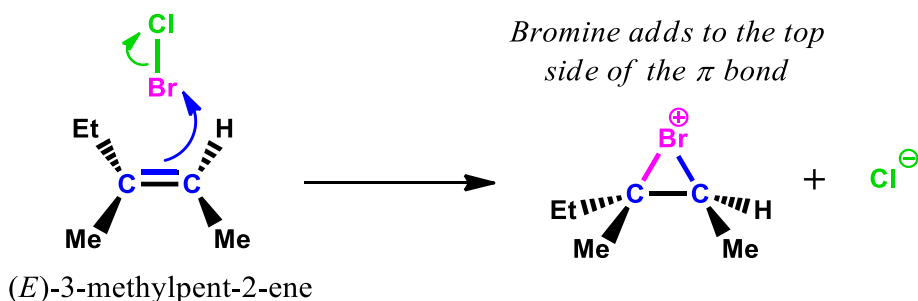
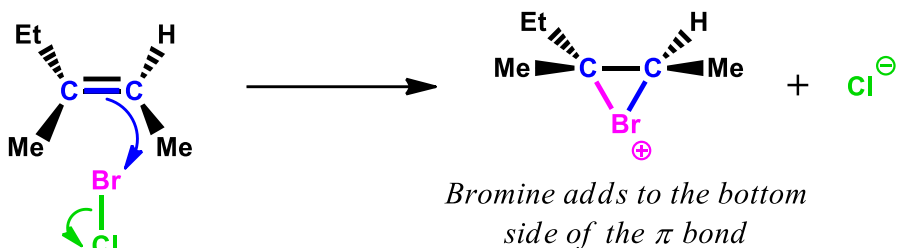
Bromine adds to the top side of the π bond

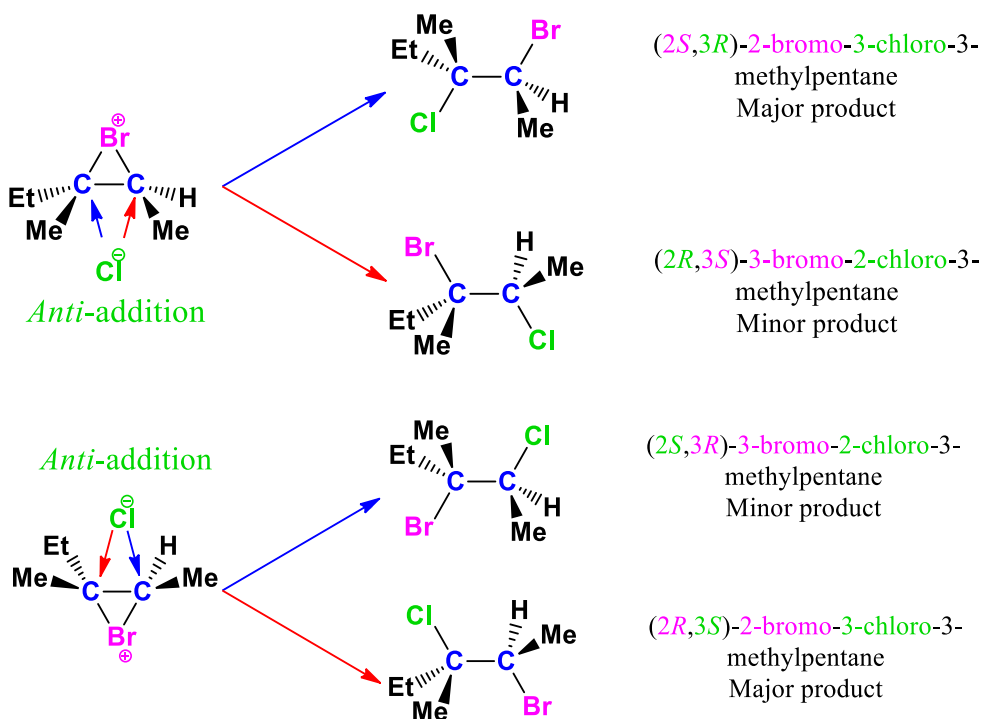
Br
Et
C
C
H
Me
Me
+
$Cl^{\ominus}$

(*E*)-3-methylpent-2-ene

(*E*)-3-methylpent-2-ene

Et H C C Me Me Br Cl → Et H Me C C Me Br ⊕ + Cl⊖

Bromine adds to the bottom side of the π bond

Step two

In the next step , the chloride ion would preferentially attack the most substituted carbon atoms attached to the bromonium ion via *anti*-addition.

The overall reaction would then give two racemic mixtures with one more predominant. As a result , halogenation of asymmetrical alkenes is a **non-stereoselective** reaction.

Major products
Racemic mixture

(2*R*,3*S*)-2-bromo-3-chloro-3-methylpentane

(2*S*,3*R*)-2-bromo-3-chloro-3-methylpentane

Chlorine is added on the top side

Chlorine is added on the bottom side

BrCl

BrCl

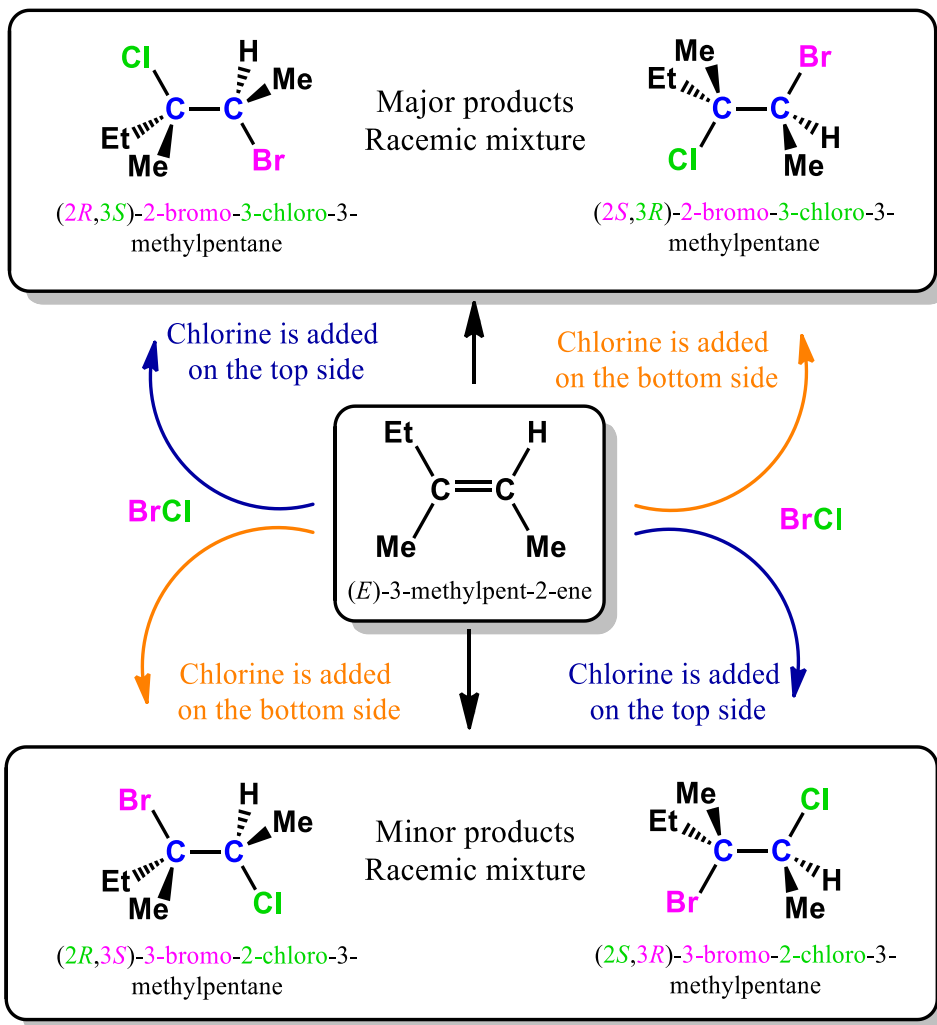
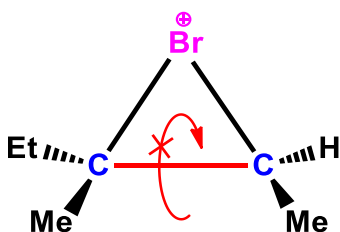
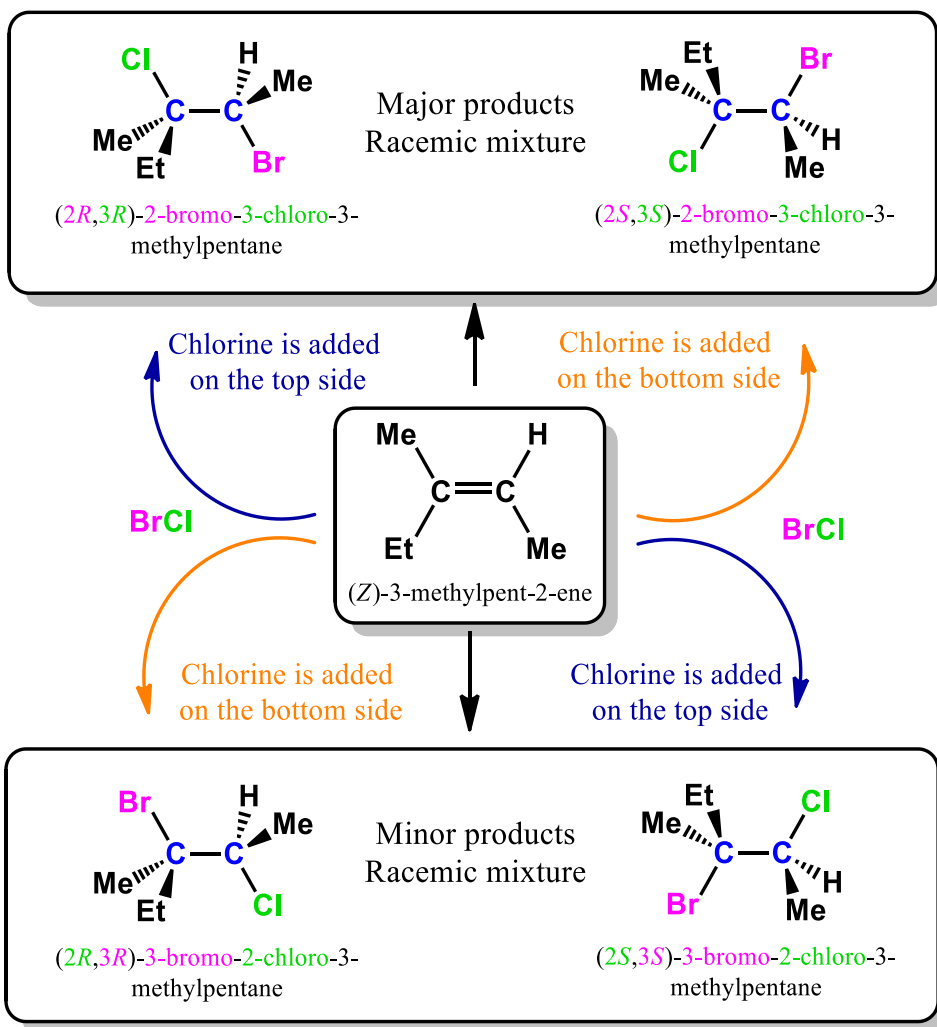
(*E*)-3-methylpent-2-ene

Chlorine is added on the bottom side

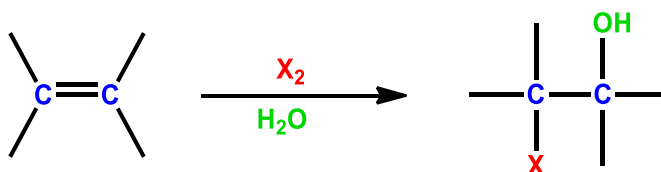
Chlorine is added on the top side

Minor products
Racemic mixture

(2*R*,3*S*)-3-bromo-2-chloro-3-methylpentane

(2*S*,3*R*)-3-bromo-2-chloro-3-methylpentane

Because the intermediate involved is cyclc, free rotation around σ bond connecting the two carbon atoms attached to bromonium ion is not p ossible. Consequently, (*Z*)-3-methylpent-2-ene reacts with bromine chloride to yield the same products obtained when using (*E*)-3-methylpent-2-ene. Nevertheless, these compounds would have different stereochemistry, which makes this reaction **stereospecific**.

Rotation around σ bond is not allowed.

III. 4. 2. 5. Hypohalogenation Reaction

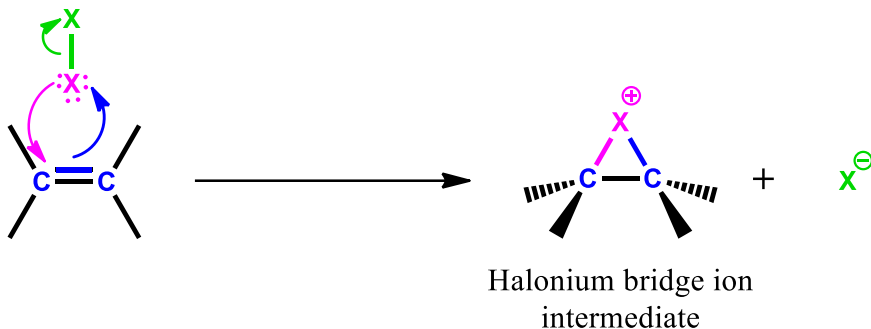
Hypohalogenation is an electrophilic reaction that consists in converting alkenes into halohydrins. This reaction take place when using halogens such as Br_2 or Cl_2 in excess of water.

C=C
X_2
H_2O
OH
C
C
X

Mechanism

Just like alkenes halogenation, hypohalogenation proceeds in two steps and involves a halonium ion bridge.

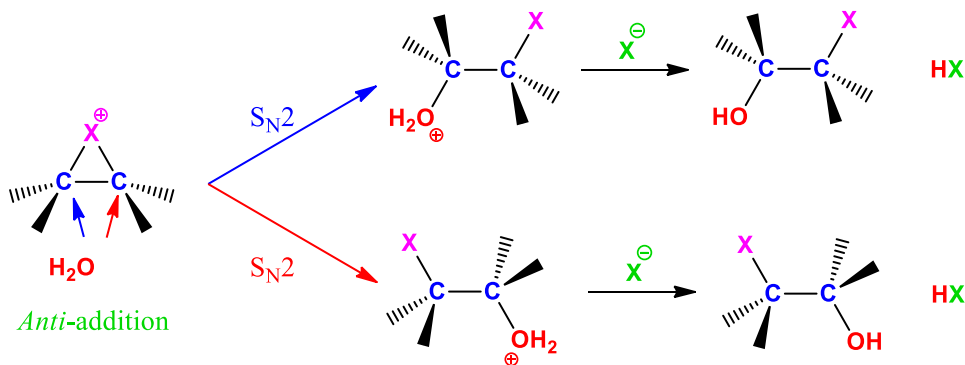
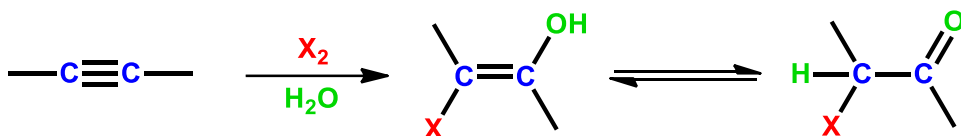
First step

The first step consists in forming a halonium ion bridge intermediate.

Halonium bridge ion intermediate

Second step

In the next step, a water molecule will preferentially attack the most substituted carbon atom, which leads to an oxonium intermediate. This nucleophilic attack proceeds exclusively via *anti*-addition.

S_N2 S_N2 H_2O HX   HX

Anti-addition

In case of alkynes, the reaction initially produces a *trans*-halogenated enol, which then tautomerizes to give α-halo carbonyl compounds.

X_2 H_2O

Regiochemistry and Stereochemistry

Hypohalogenation of asymmetrical alkenes is a **regioselective reaction** that follows Markovnikov's rule where the major product is the one obtained when hydroxy group adds to the most substituted carbon atom, and a **regiospecific** reaction that proceeds exclusively via *anti*-addition. In terms of stereochemistry, hypohalogenation of asymmetrical alkenes is **non-stereoselective reaction** that gives a mixture of stereoisomers since the halogen can add from either sides of the π bond and the nucleophile.

➲ ***Example***

First step

Bromine adds to the top side of the π bond

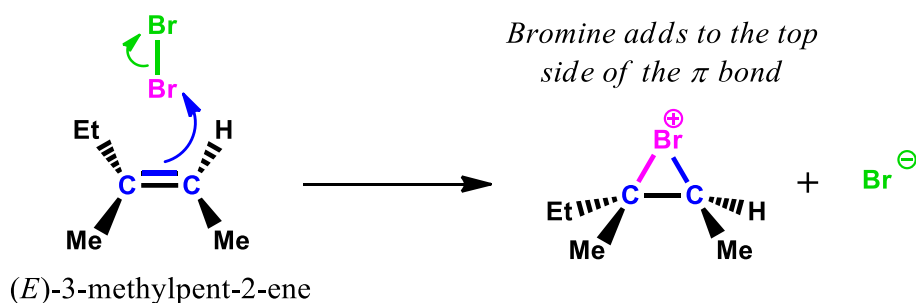
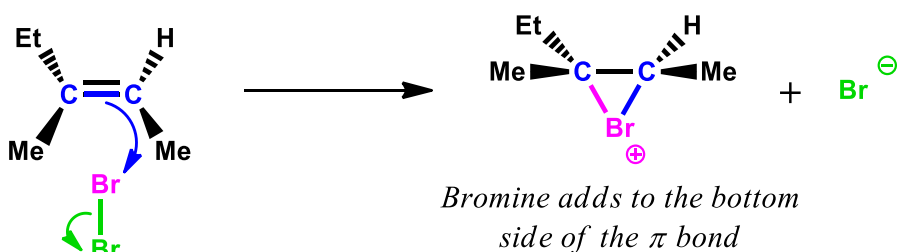
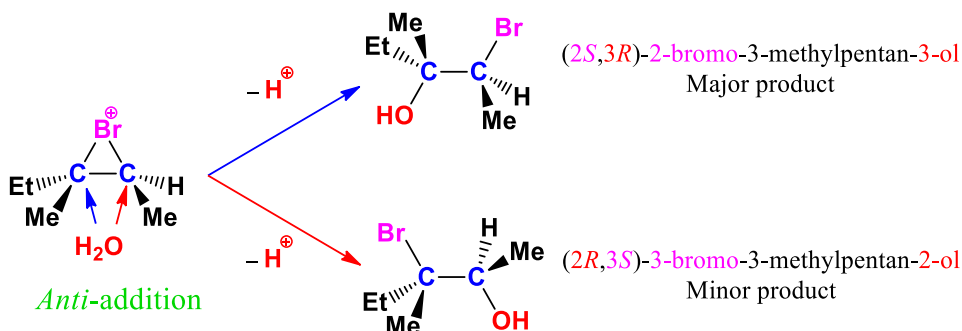
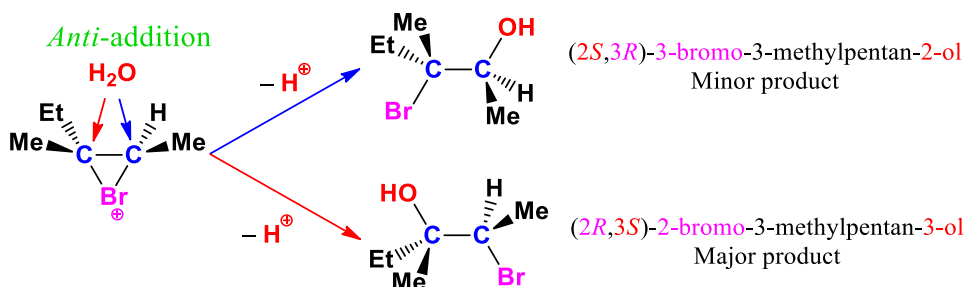
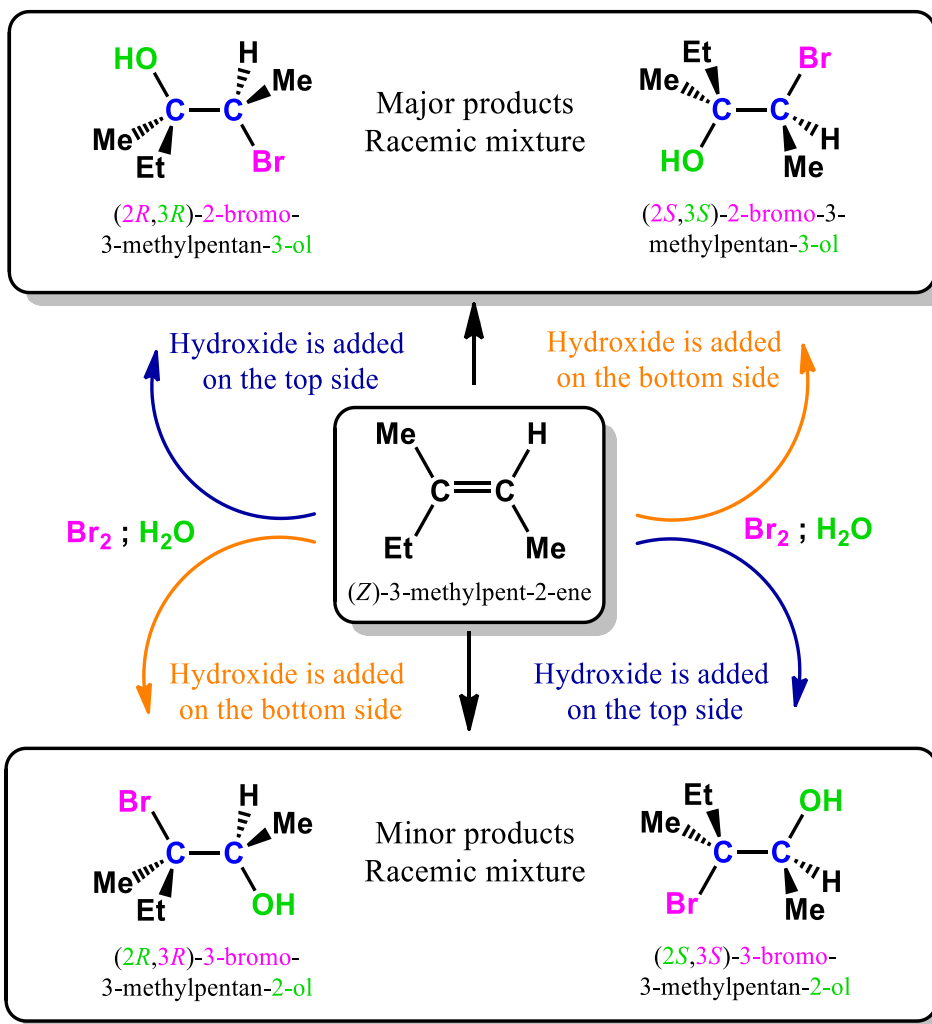
(*E*)-3-methylpent-2-ene

(*E*)-3-methylpent-2-ene

Second step

Anti-addition

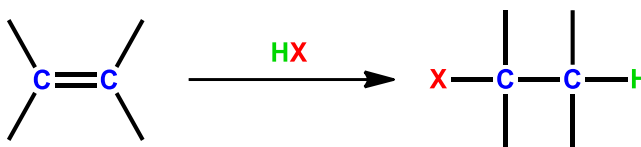
(2*S*,3*R*)-3-bromo-3-methylpentan-2-ol
Minor product

(2*R*,3*S*)-2-bromo-3-methylpentan-3-ol
Major product

Moreover, because free rotation around σ bond is restricted, the bromohydrins obtained from (*Z*)-3-methylpent-2-ene would have different stereochemistry making this reaction **stereospecific**.

III. 4. 2. 6. Hydrohalogenation Reaction

Hydrohalogenation is an electrophilic addition that consists in adding a hydrogen atom and a halogen to two carbon atoms of a substrate that are connected with a multiple bond. These carbon atoms may or may not be vicinal depending upon the structure of the substrate and possibility of carbocation rearrangements. Hydrohalogenation reaction involves hydrogen halide acids such as HI, HBr, and HCl where hydrogen acts as an electrophile while halogens act as nucleophiles.

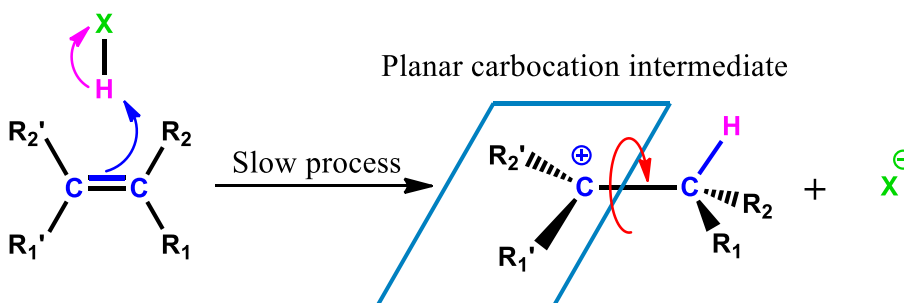
Alkenes

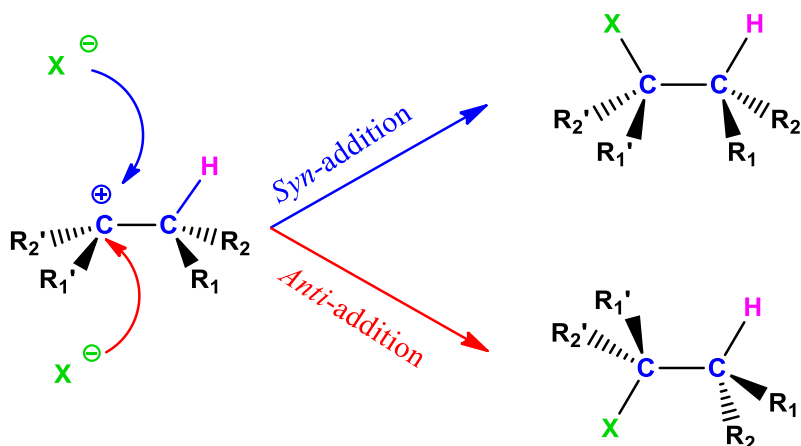
In case of alkenes, the hydrogen atom and halide are generally added to the vicinal sp^2 carbon atoms. However, sometimes the addition occurs on non-vicinal carbon atoms due to carbocation rearrangement.

$$C=C \xrightarrow{HX} X-C-C-H$$

Mechanism

Hydrohalogenation reaction proceeds in two steps and involves a carbocation intermediate.

Step one

The first step is a slow process in which the π bond breaks and abstracts a hydrogen proton from the hydrogen halide resulting in a carbocation intermediate and a halide ion.

Step two

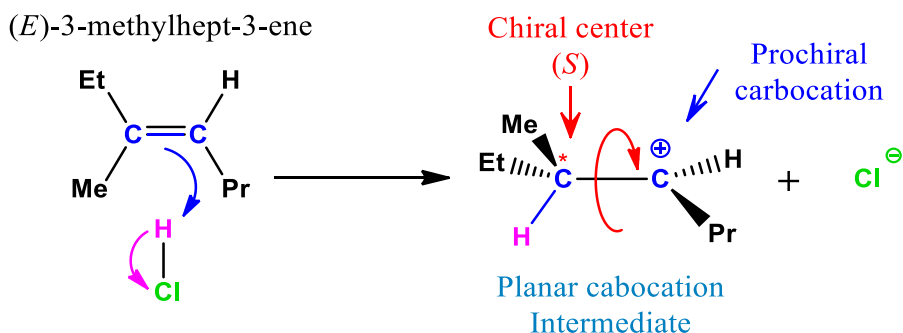
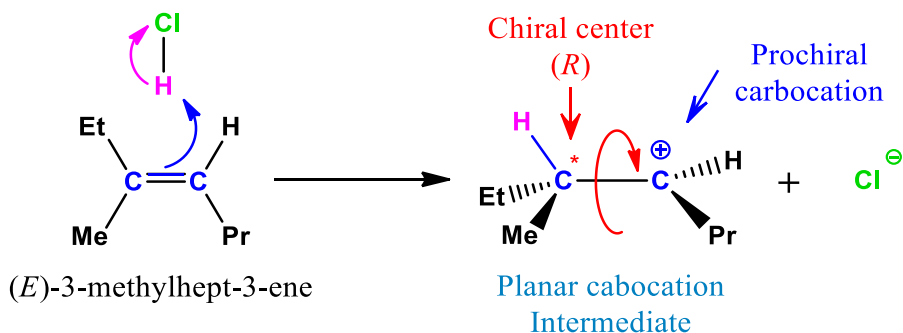
The second step is a fast process where the nucleophilic halide attacks the carbocation from either sides. This process proceeds via *syn*-addition and *anti*-addition.

Regiochemistry and Stereochemistry

Hydrohalogenation addition is a **regioselective reaction** that follows Markovnikov's rule. In this reaction, the hydrogen atom “electrophile” preferentially adds to the least substituted carbon atom while the nucleophilic halide adds to the most substituted one. Moreover, hydrogen atom and halide can be added to the substrate via *syn*-addition or *anti*-addition resulting in two different configurations on the corresponding stereocenter and therefore hydrohalogenation is a **non-regiospecific, non-stereoselective reaction**. Moreover, since this reaction involve a carbocation intermediate where the free rotation around σ bond is not restricted, the initial configuration of the alkene is not preserved and as a result, hydrohalogenation of asymmetrical alkenes is **non-stereospecific reaction**.

➲ ***Example***

Hydrochlorination of (*E*)-3-methylhept-3-ene

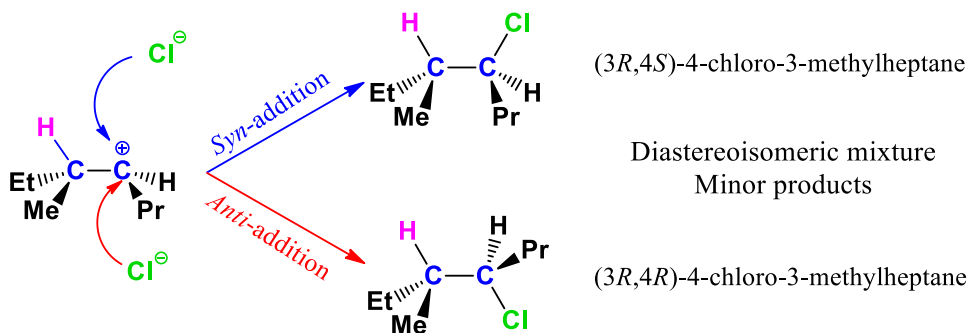
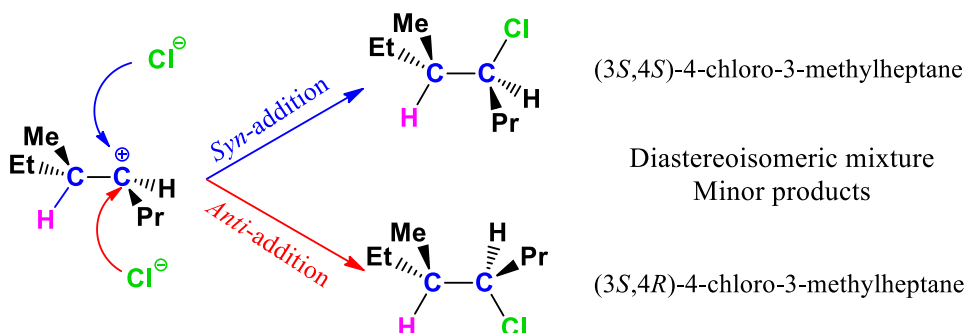
First step

The first step consists in the protonation of one sp^2 carbon atom and the formation of a carbocation intermediate and the formation of a chloride ion. In this case, the hydrogen atom was added to the most substituted carbon atom and thus, producing the least stable carbocation. Moreover, hydrogen proton can add from either sides of the π bond, which leads to the formation of two different stereocenters.

Second step

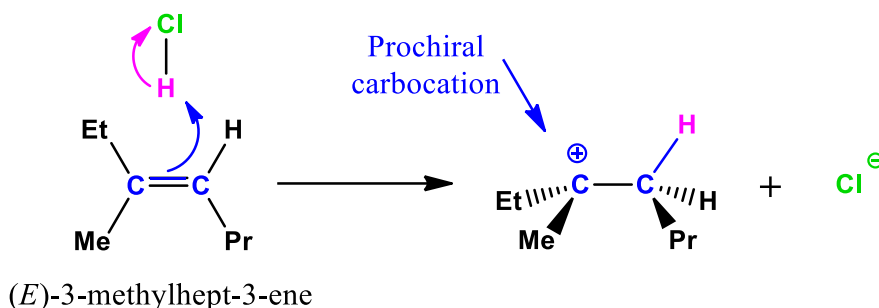
In this step, the chlorideion would attack the carbocation from either sides resulting in a mixture of two diastereoisomers. In this case, the two diastereoisomers formed are the minor products since they do not obey Markovnikov's rule.

(3*S*,4*S*)-4-chloro-3-methylheptane

Diastereoisomeric mixture
Minor products

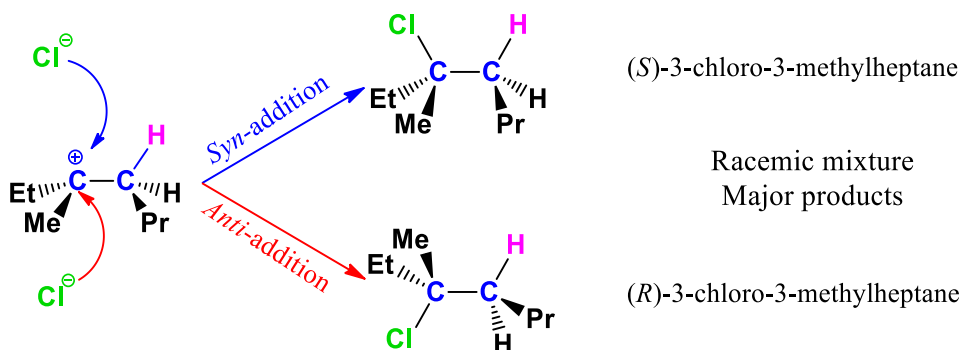
(3*S*,4*R*)-4-chloro-3-methylheptane

In the second case, the hydrogen atom adds to the least substituted carbon atom, which leads to the formation of the most stable carbocation intermediate. In this case, Markovnikov's rule is respected.

Prochiral carbocation

(*E*)-3-methylhept-3-ene

Next, chloride would attacks the carbocation from either sidesleading to a racemic mixture. In this case, Markovnikov's rule is respected and therefore, the racemate formed is the major compound.

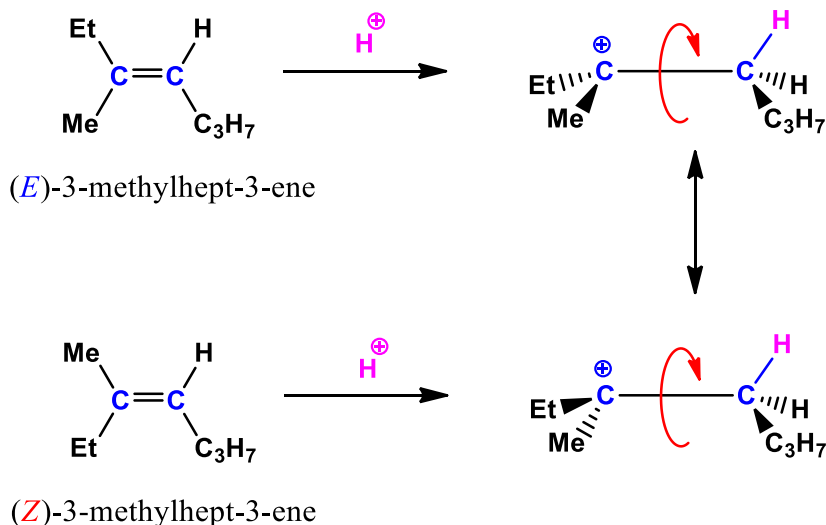
(*S*)-3-chloro-3-methylheptane

Racemic mixture
Major products

(*R*)-3-chloro-3-methylheptane

Since the first step of hydrohalogenation reaction requires the rupture of the double bond, the free rotation about σ bond would no longer be restricted. Consequently, the stereochemical configuration of the substrate would not affect the stereochemical configuration of thefinal products. As a result, even when using the

diastereoisomer (*Z*)-3-methylhept-3-ene, the reaction would give the same products that were obtained when using (*E*)-3-methylhept-3-ene.

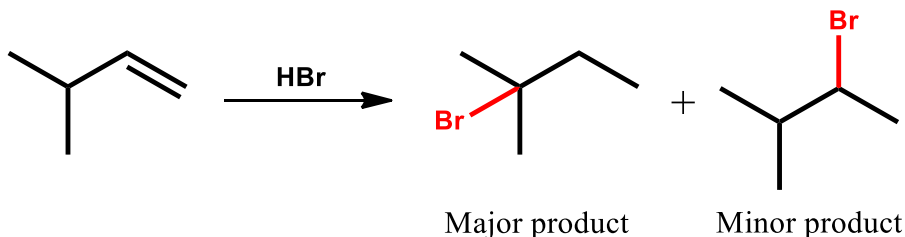
(*E*)-3-methylhept-3-ene

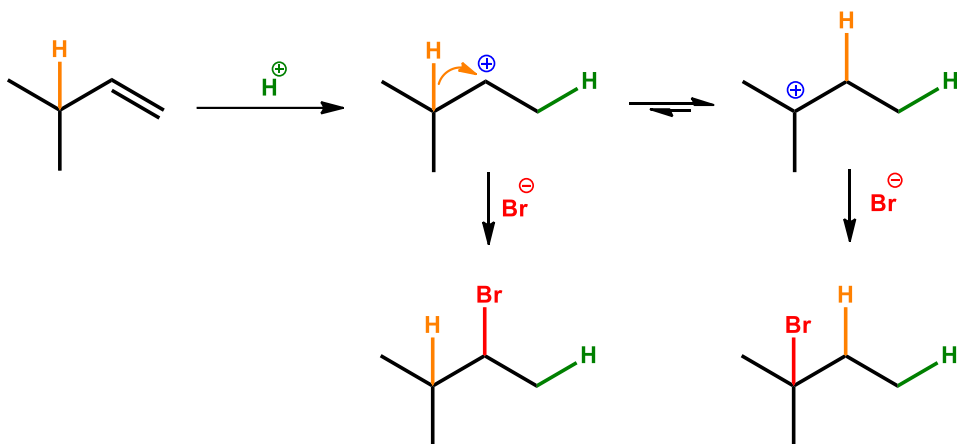
(*Z*)-3-methylhept-3-ene

Carbocation rearrangement

Since hydrohalogenation involves a carbocation intermediate, it is important to take into account the possibility of carbocation rearrangements, which affects the regiochemistry of the reaction.

➲ ***Example***

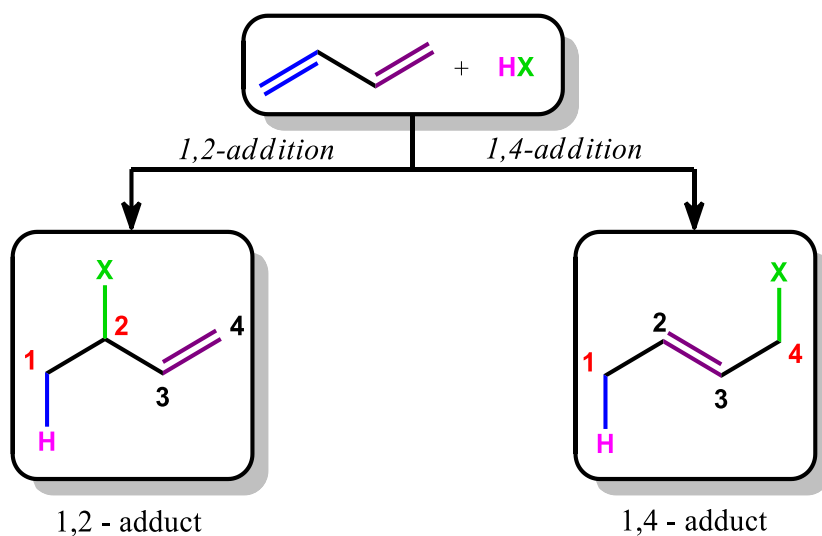
Hydrobromination of 3-methylbut-1-ene yields two constitutional isomers "regioisomers". In this case, carbocation rearrangement

Major product   Minor product

In this example, when the electrophilic hydrogen adds to the least substituted sp^2 carbon atom, a secondary carbocation forms on the vicinal carbon atom. In this case, 1,2-hydride shift can take place whereby the positive charge gets delocalized

to a tertiary carbon, which is more stable than the initial secondary carbocation As a result, the nucleophile addition is more likely to capture the tertiary carbocation leading to the major product.

Conjugated Dienes

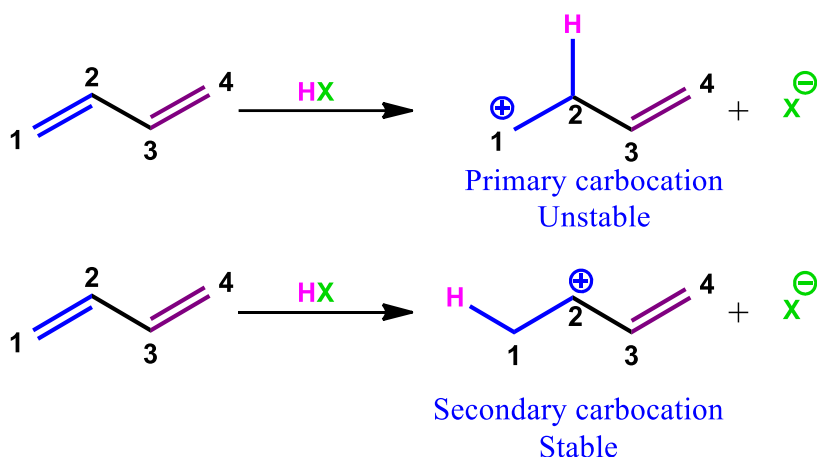
Depending upon the reaction conditions, h ydrohalogenation of conjugated dienes can proceed in two different manners; 1,2–addition and 1,4–addition.

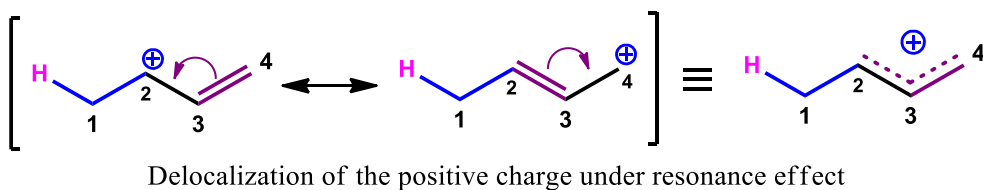
1,2 - adduct

1,4 - adduct

Mechanism

Just like regular alkenes, hydrohalogenation of conjugate dienes proceeds in two steps and passes through the formation of a carbocation intermediate. However, because conjugated dienes contain two double bonds, carbocation rearrangement via resonance provides two positions where the addition of halide can take place.

Step one

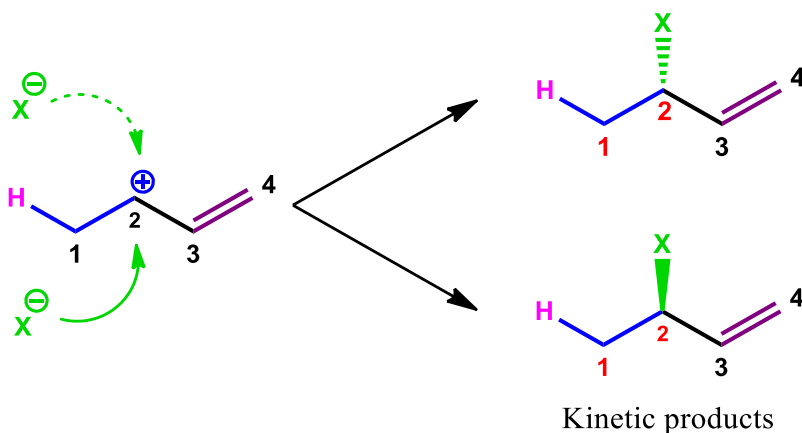
Hydrohalogenation of conjugated dienes begins with the addition of a hydrogen proton to the substrate. At this point, one of the double bonds breaks and attacks the electrophilic hydrogen proton resulting in the formation of a carbocation on the vicinal carbon atom.

The intermediate formed in this case is stabilized by resonance effect, which delocalizes the positive charge on position 1 and 4.

Delocalization of the positive charge under resonance effect

Second step

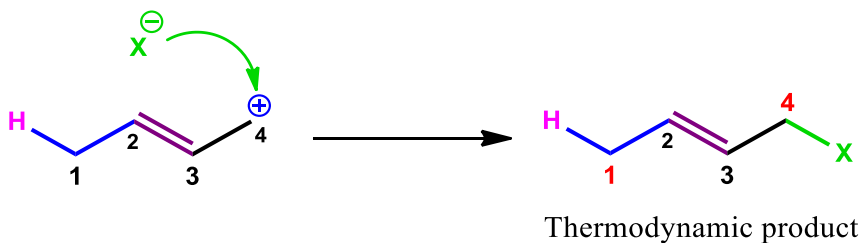
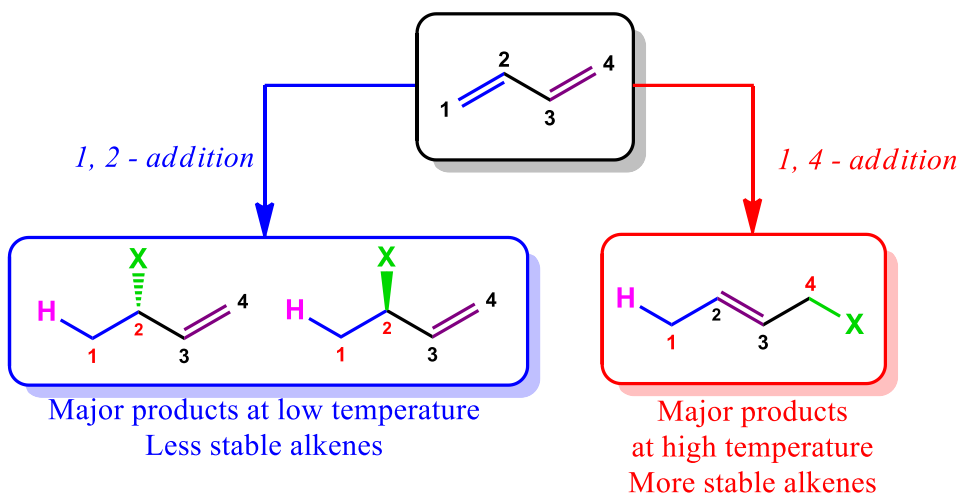
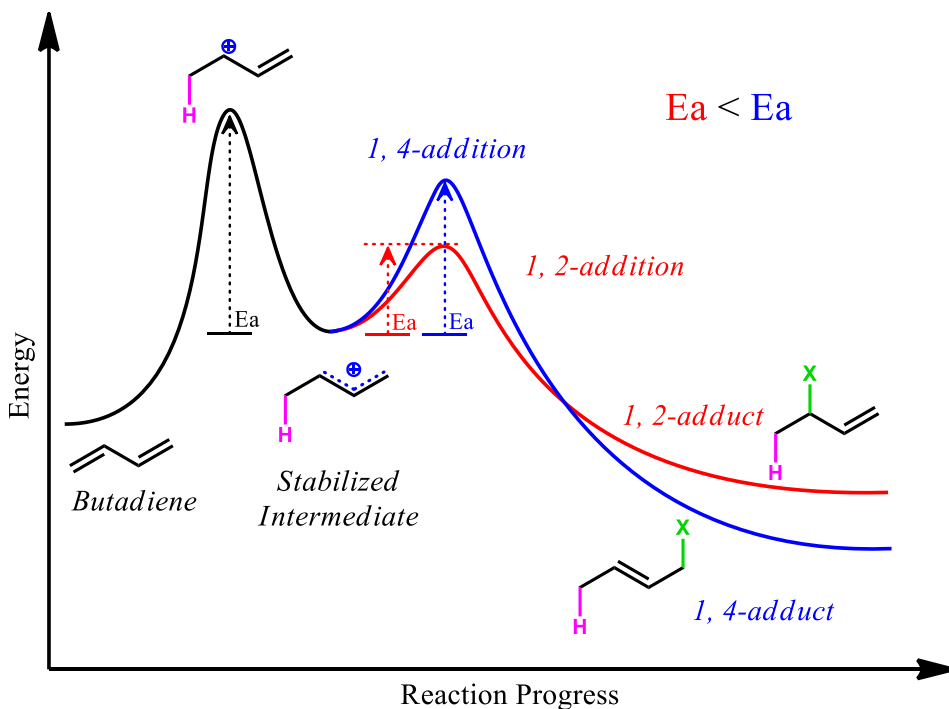
Since the positive charge is delocalized on two position, the nucleophilic halide can either add to the carbocation on position 2, which will lead to the formation of the kinetic product or to the carbocation on position 4, which will give the thermodynamic product.

1, 2–addition

1, 2 –addition describes the reaction pathway where both groups add to vicinal carbon atoms. This type of addition is more f avorable at low temperature, wh ich restricts carbocation rearrangement. In this case, the halide ion would still be near to the hydrogen atom that got added to the substrate, consequently, the addition is more likely to occur on the second carbon atom due to the proximity effect. In this case, the product obtained is called the 1, 2 –adduct, which is also known as the kinetic product.

Kinetic products

1,4–addition

1, 4–addition refers to the reaction pathway where hydrogen atom adds to carbon 1 while the halide ion captures the rearranged carbocation on position 4. In contrast to 1,2–addition, 1,4–addition is more favorable at high temperature which facilitates carbocation rearrangement and therefore, the products obtained from this reaction are called the thermodynamic pr oducts, which are more stable than the kinetic products.

Thermodynamic product

The diagram below demonstrate the difference between 1,2–addition and 1,4–addition for butadiene hydrohalogenation. 1,2–addition requires less activating energy but leads to the formation of a less stable haloalkenes, on the other hand, 1,4–addition requires additional energy but produces more stable adducts.

Regiochemistry and Stereochemistry

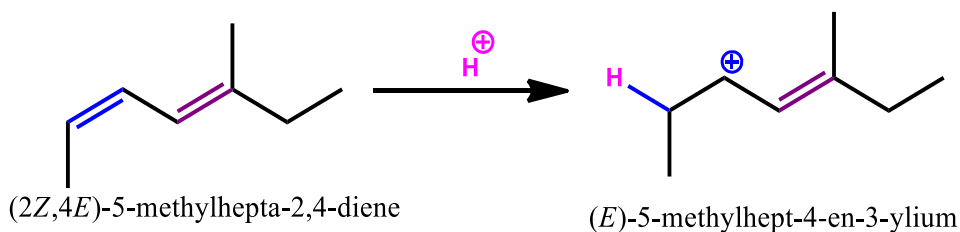
Generally, hydrohalogenation of conjugated dienes is similar to hydrohalogenation of alkenes in terms of stereoselectivity and stereospecificity. Nevertheless, the regiochemistry differs from alkenes to conjugated dienes due to resonance effect.

➲ ***Example***

Hydrobromination of (2*Z*,4*E*)-5-methylhepta-2,4-diene.

First Step

(2*Z*,4*E*)-5-methylhepta-2,4-diene

(*E*)-5-methylhept-4-en-3-ylium

The intermediate formed may acquire a different stereochemistry before the delocalization of the positive charge when rotation about σ bond between the carbocation and the sp^2 carbon is possible. As a result, different forms of intermediates may be valid.

1 (*E*)-5-methylhept-4-en-3-ylium

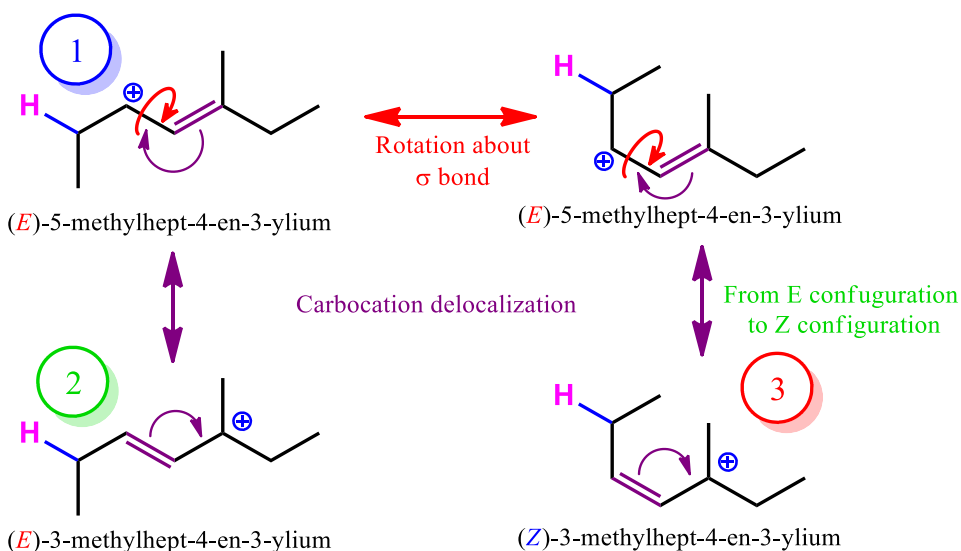
Rotation about σ bond

(*E*)-5-methylhept-4-en-3-ylium

Carbocation delocalization

From E configuration to Z configuration

2 (*E*)-3-methylhept-4-en-3-ylium

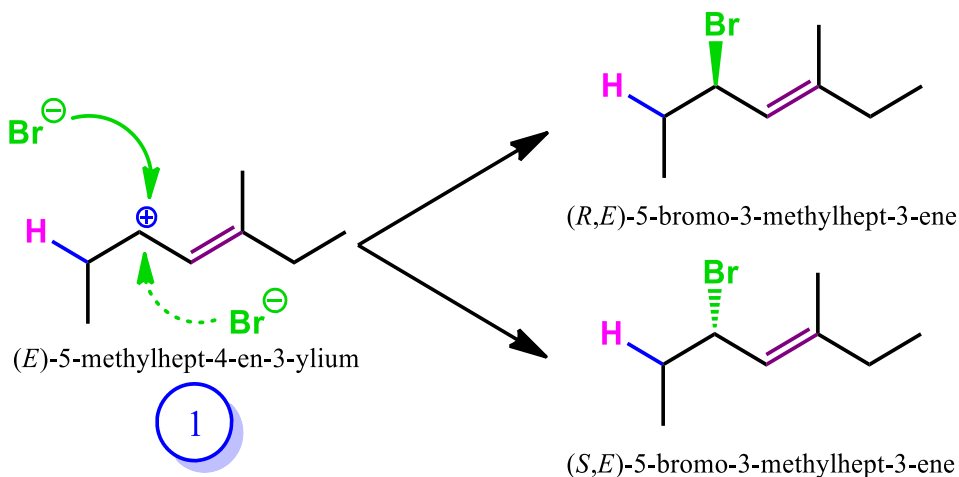
3 (*Z*)-3-methylhept-4-en-3-ylium

Second Step

If the reaction is carried out at low temperature, 1,2–adducts, which can be obtained from the intermediate 1 would predominate over 1, 4–adducts.

(*E*)-5-methylhept-4-en-3-ylium

1

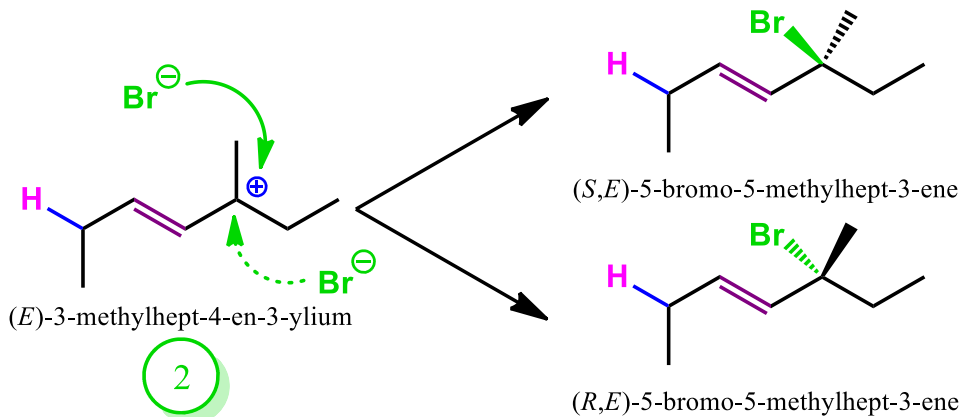
(*R*,*E*)-5-bromo-3-methylhept-3-ene

(*S*,*E*)-5-bromo-3-methylhept-3-ene

On the other hand, if the reaction is carried out at high temperature , the thermodynamic products "1,4–adducts", which can be obtained from intermediate 2 and 3 would prevail.

(*E*)-3-methylhept-4-en-3-ylium

2

(*S*,*E*)-5-bromo-5-methylhept-3-ene

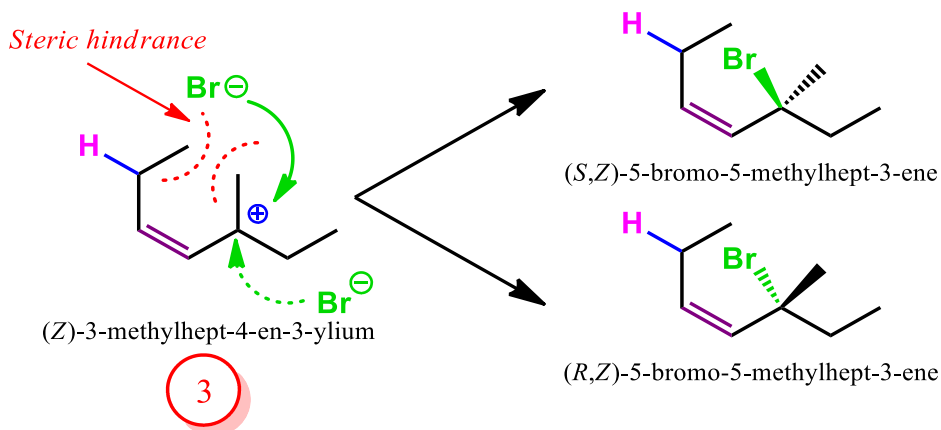
(*R*,*E*)-5-bromo-5-methylhept-3-ene

In case (*Z*)-3-methylhept-4-en-3-ylium is observed, products obtained from it will be produced at a very low yield due to their instability caused by the steric hindrance of Z configuration.

Steric hindrance

(*Z*)-3-methylhept-4-en-3-ylium

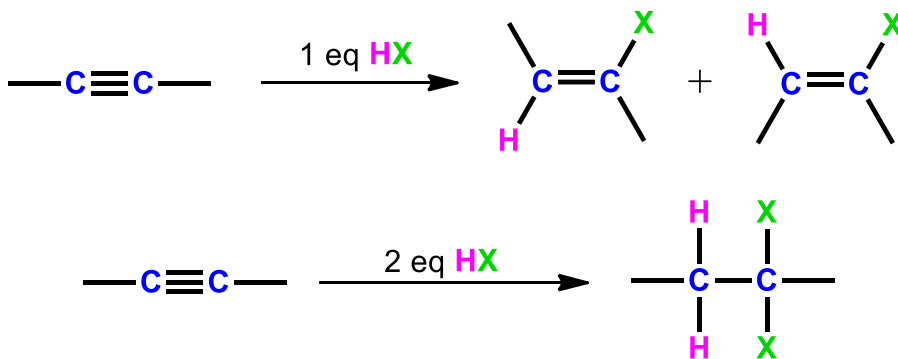
3

(*S*,*Z*)-5-bromo-5-methylhept-3-ene

(*R*,*Z*)-5-bromo-5-methylhept-3-ene

Alkynes

Alkynes react with hydrogen halides in similar way to alkenes. If one molecular equivalent of an alkyne reacts with one molecular equivalent of hydrogen halide, a vinyl halide is obtained. On the other hand, treating an alkyne with two molecular equivalents of a hydrogen halide would produce a geminal alkyl dihalide.

1 eq HX

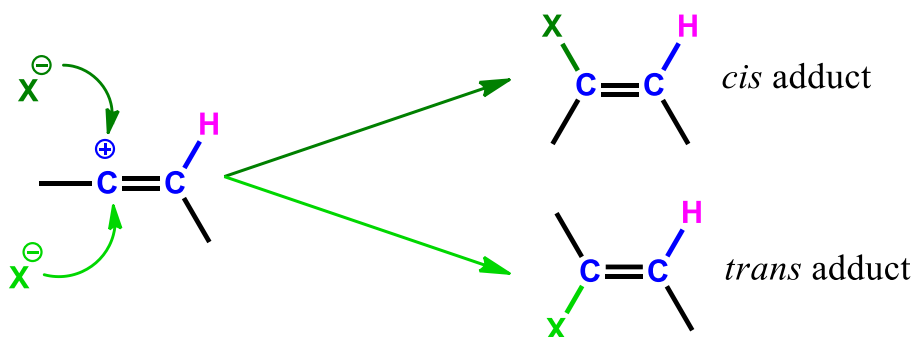
2 eq HX

Mechanism

Hydrohalogenation of alkynes with one molecular equivalent gives mainly *trans* vinyl halides. Chemists have proposed two mechanisms to describe how hydrogen halides add to alkynes. The first one proceeds in two steps and involves alkenyl carbocation intermediate.

Alkenyl carbocation intermediate

In this case, the nucleophilic halide can capture the carbocation from either sides resulting in a mixture of *cis* and *trans* vinyl halides.

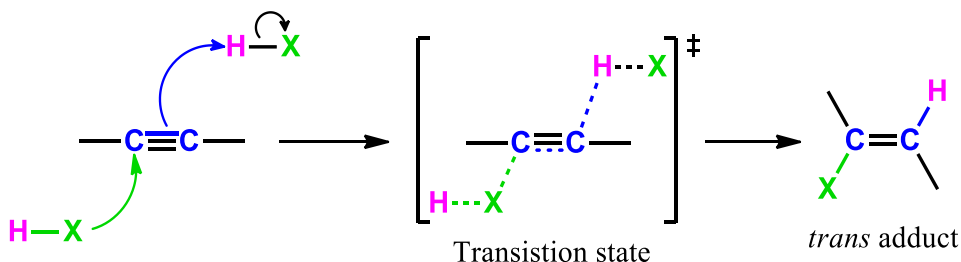
cis adduct

trans adduct

This mechanism is generally disfavo red since sp^2 hybridized carbocations are not stable which makes alkynes less reactive than alkenes.

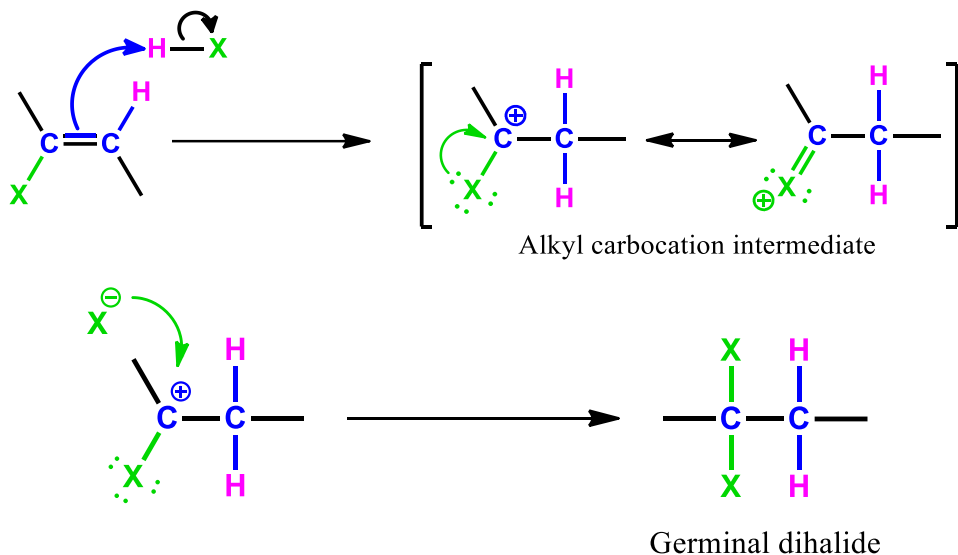
The second mechanism, which was proposed based upon experiments and kinetic data, is a termolecular process that proceeds ina concerted manner. In this case, the hydrogen atom adds to the alkyne at the same time as the halide, which makes the reaction rate first order with respect to the substrate and second order with respect to the hydrogen halide termolecular.

$$Rate = K[\text{Alkyne}][\text{HX}]^2$$

Transistion state

trans adduct

Vinyl halides tend to be less reactive than alkenes, which makes it possible to isolate the product and prevent further hydr ohalogenation. However, if two molecular equivalents of hydrogen halide adds to the alkynes, the final product would be germinal dihalide. In this case, although the halogen is electronegative, it can stabilize the carbocation via donating mesomeric effect +*M*. As a result, carbocation forms on the carbon attached to the halogen, which gives rise to the formation of germinal dihalide.

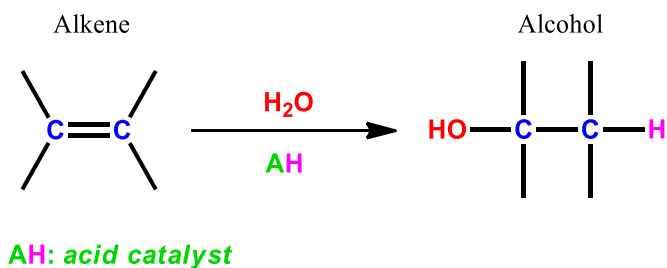
Alkyl carbocation intermediate

Germinal dihalide

III. 4. 2. 7. Acid Catalyzed Hydration

Acid catalyzed hydration is an electrophilic reaction whereby a water molecule adds to an unsaturated hydrocarbon under acidic conditions.

Alkenes

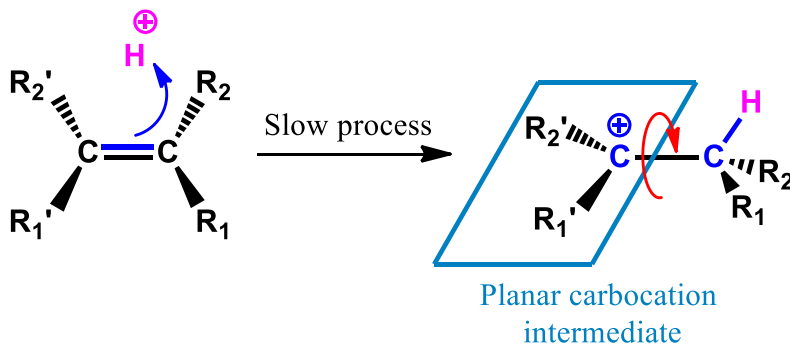
Acid catalyzed hydration of alkenes is a very useful method to synthesize alcohols.

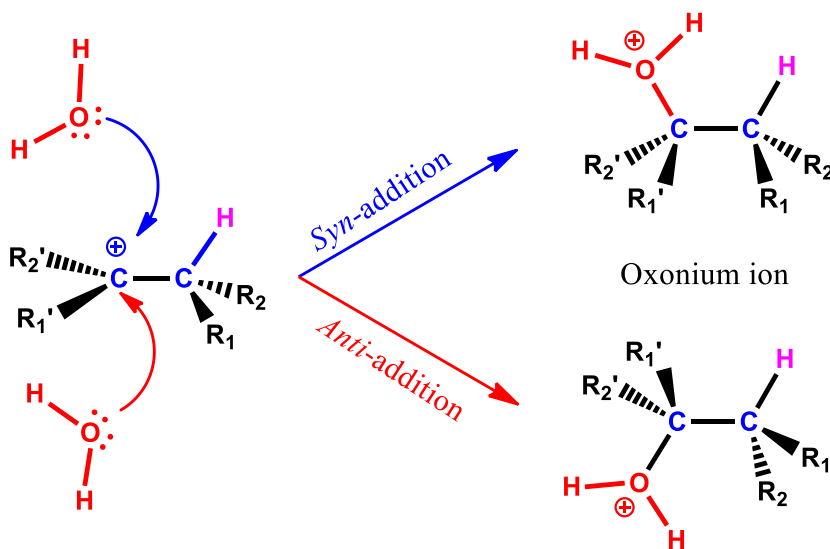
Alkene — H_2O, AH → Alcohol

AH: ***acid catalyst***

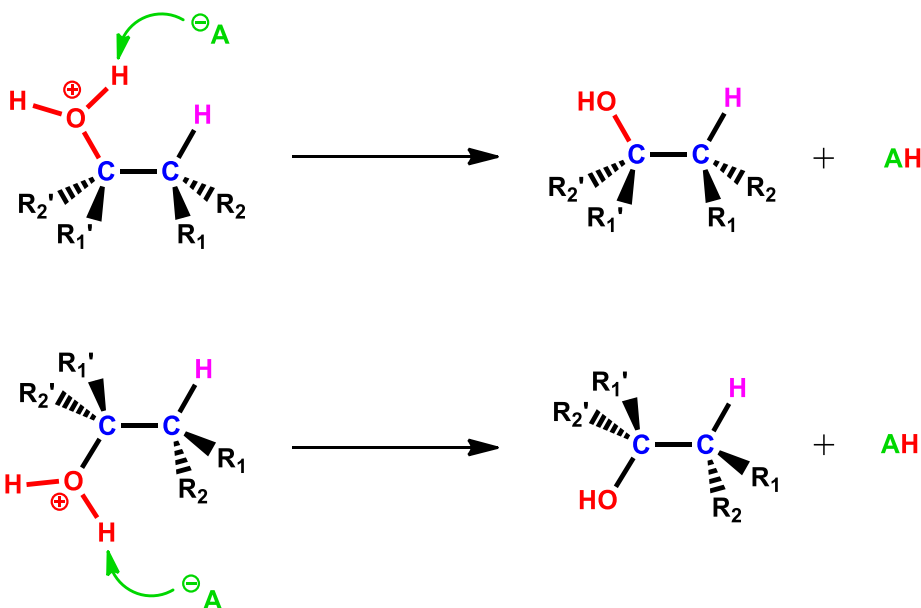
Mechanism

Acid catalyzed hydration of alkenes proceeds in three steps and involve carbocation intermediate.

Step one

The first step consists in protonating the double bond, which leads to the formation of a carbocation intermediate.

Step two

The second step is characterized by the nucleophilic a ddition of a water molecule to the carbocation intermediate from either sides resulting in an oxonium ion.

Step three

In the final step, a base “the conjugate base of the acid catalyst, or a water molecule” would abstract a hydrogen proton from the oxonium ion, which leads to the formation of an alcohol.

Regiochemistry and Stereochemistry

Acid catalyzed hydration of alkenes is a **regioselective** reaction that follows Markovnikov's rule where hydrogen proton preferentially adds to the least substituted sp ^{2} carbon atom in order to form a stable carbocation intermediate. Moreover, since the nucleophilic addition of water can take place on either sides of the carbocation, two stereoisomers may form and therefore, this reaction is **non-stereoselective**. Furthermore, acid catalyzed hydration of asymmetrical alkenes is a **non-stereospecific** reaction where E and Z isomers produce the same stereoisomers, this happens because free rotation around σ bond between the carbocation and the carbon atom that received a hydrogen proton is not restricted.

➲ ***Example***

Acid catalyzed hydration of (*E*)-3-methyloct-3-ene with dilute sulfuric acid.

Step one

In the first step, a hydrogen proton adds to either sp ^{2} carbon atoms as the π bond breaks resulting in a planar carbocation intermediate. According to Markovnikov's rule, the hydrogen proton preferentially adds to the least substituted sp ^{2} carbon atom in order to create the most stabilized carbocation intermediate.

More stable

Slow process

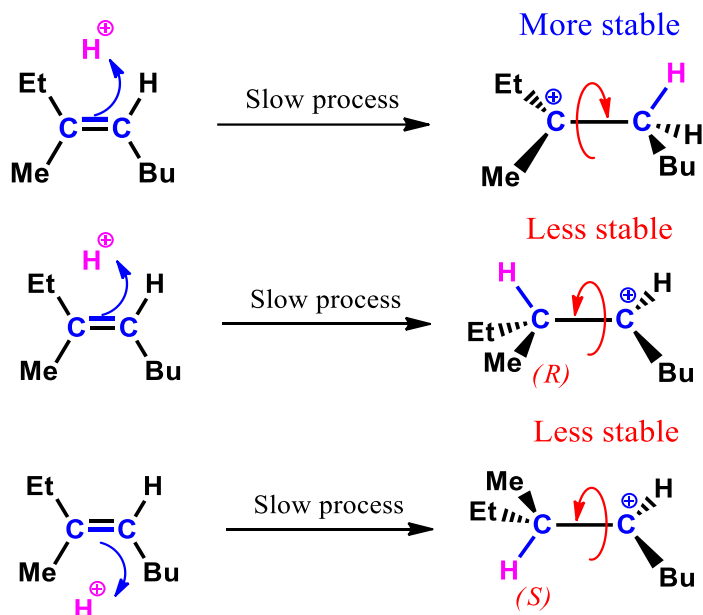
Less stable

Slow process

(R)

Less stable

Slow process

(S)

Step two and three

The next step involves nucleophilic addition of a water molecule to the carbocation from either sides resulting in an oxonium ion intermediate, which then gets deprotonated to give the corresponding alcohol . In this example, two possible carbocation intermediate are formed. However, the tertiary carbocation is more stable than the secondary one. As a result, water molecule is more likely to add to the tertiary carbocation leading to the formation of the major product 3-methyloctan-3-ol.

Syn-addition

Anti-addition

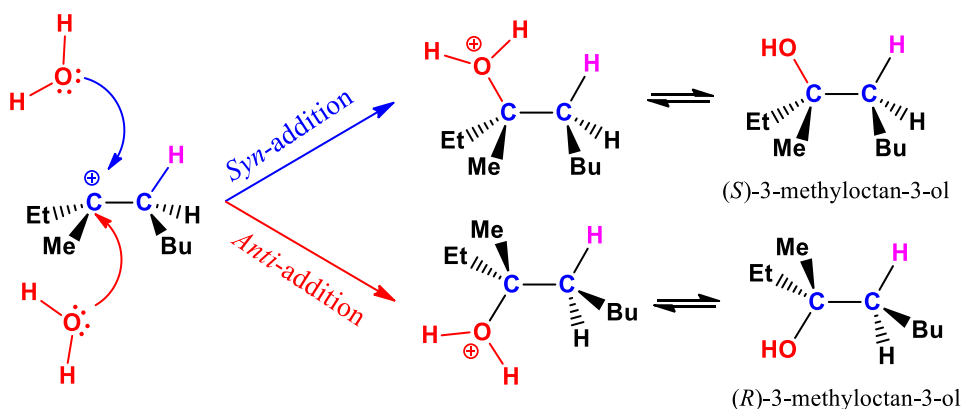
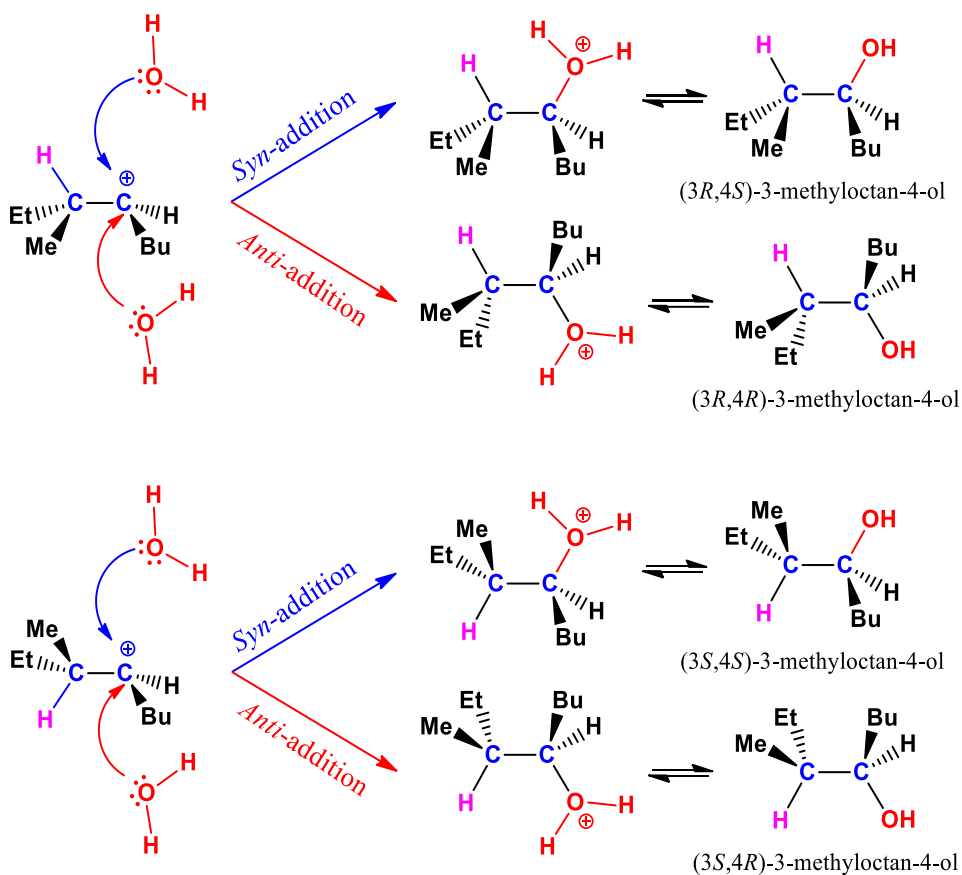
(*S*)-3-methyloctan-3-ol

(*R*)-3-methyloctan-3-ol

(3*R*,4*S*)-3-methyloctan-4-ol

(3*R*,4*R*)-3-methyloctan-4-ol

(3*S*,4*S*)-3-methyloctan-4-ol

(3*S*,4*R*)-3-methyloctan-4-ol

In case of (*Z*)-3-methyloct-3-ene, the reaction proceeds in similar way and yields the same products.

(R)-3-methyloctan-3-ol

Major products
Racimic mixture
1:1

(S)-3-methyloctan-3-ol

H_2SO_4 ; H_2O

(E)-3-methyloct-3-ene

(Z)-3-methyloct-3-ene

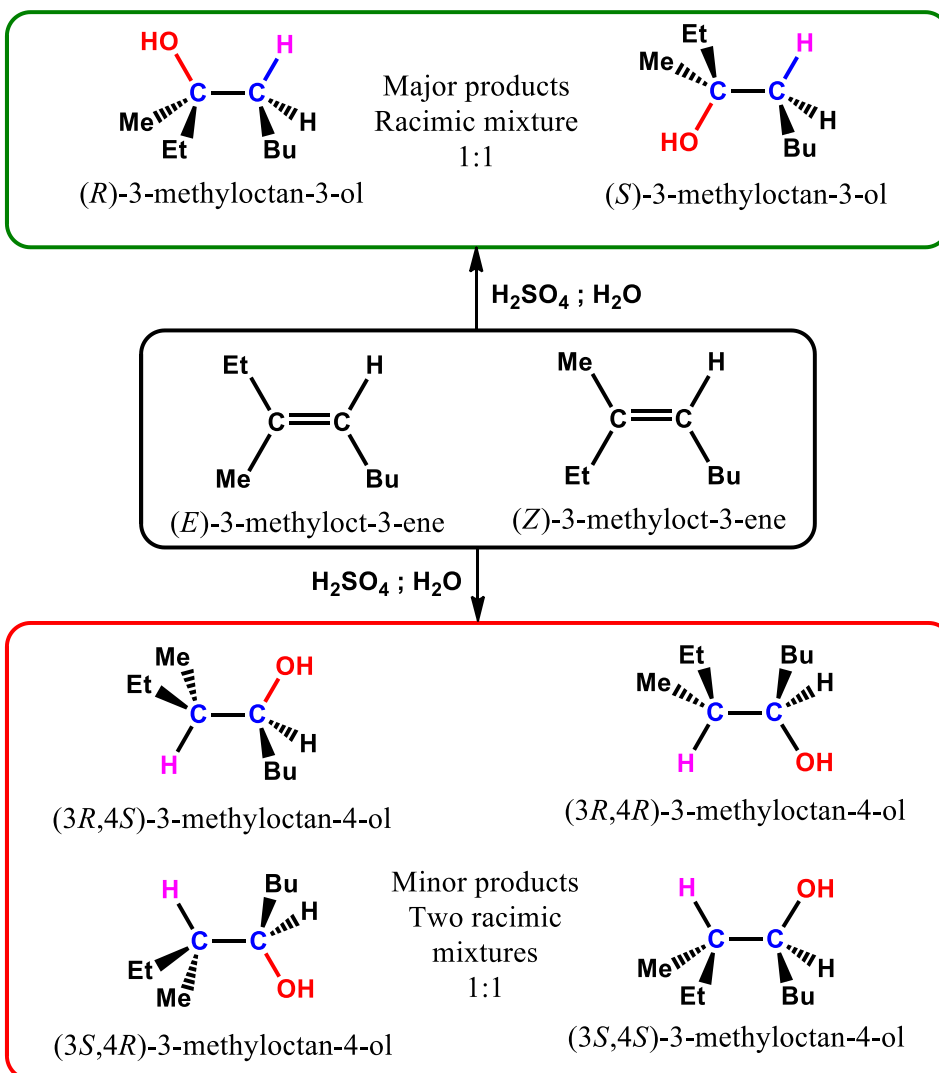
H_2SO_4 ; H_2O

(3R,4S)-3-methyloctan-4-ol

(3R,4R)-3-methyloctan-4-ol

Minor products
Two racimic
mixtures
1:1

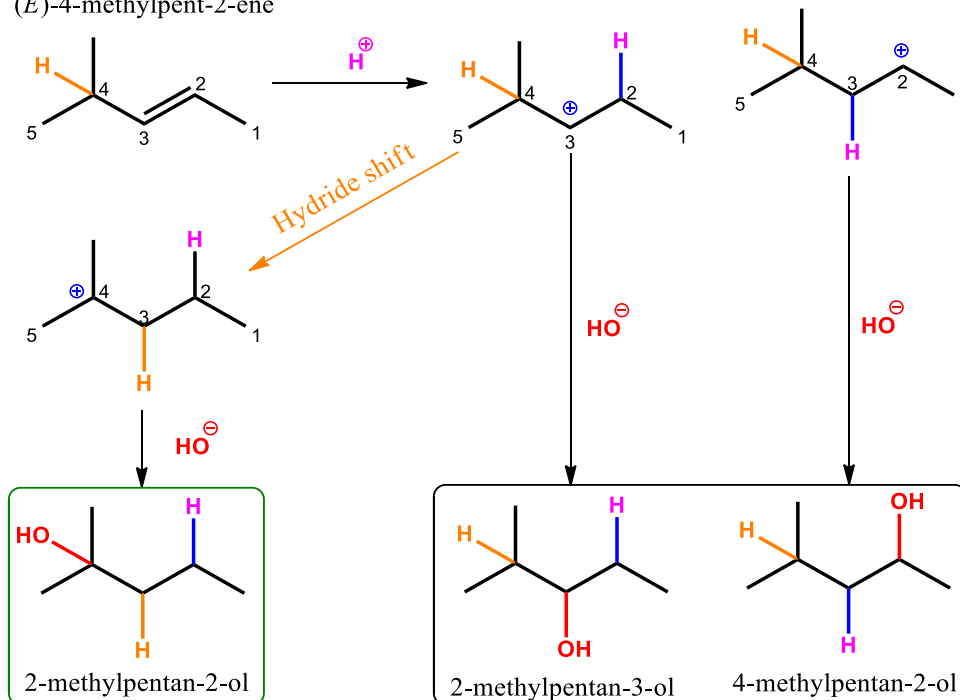
(3S,4R)-3-methyloctan-4-ol

(3S,4S)-3-methyloctan-4-ol

Carbocation rearrangement

Another property of acid catalyzed hydration is the possibility of carbocation rearrangement from a less stable state to a more stable one.

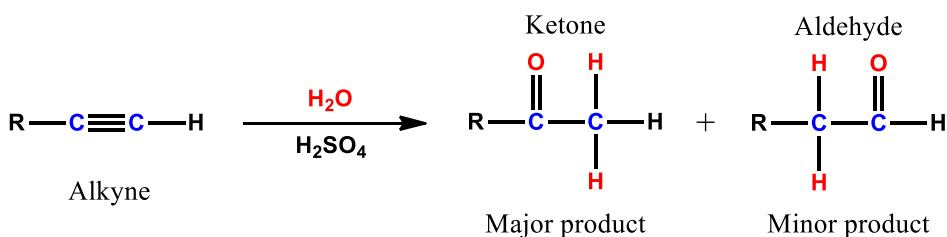
➲ ***Example***

When (*E*)-4-methylpent-2-ene is treated with a solution of sulfuric acid, three potential constitutional isomers may form. In this example, both sp^2 carbon atoms would give secondary carbocation intermediates. However, when the carbocation forms on carbon 3 there is a possibility to form a more stabilized tertiary

carbocation on position 4 via 1,2 -hydride shift. As a result, 2-methylpentan-2-ol would predominates over the other alcohols.

Alkynes

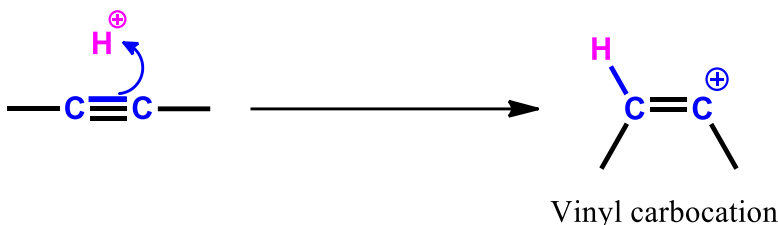
Acid catalyzed hydration of alkynes initially produces enol s, which then tautomerize into the corresponding carbonyl compound s "aldehyde or ketone". This particular reaction is carried out with aqueous sulfuric acid and it is more effective for internal alkynes. Terminal alkynes, on the other hand, tend to be less reactive toward the addition of water than internal alkynes and the reaction is usually carried out with mercuric sulfate catalyst.

$$R-C\equiv C-H \xrightarrow[H_2SO_4]{H_2O} R-C(=O)-CH_2-H + R-CH_2-C(=O)-H$$

Alkyne — Ketone (Major product) + Aldehyde (Minor product)

Mechanism

The mechanism for this reaction proceeds in three steps.

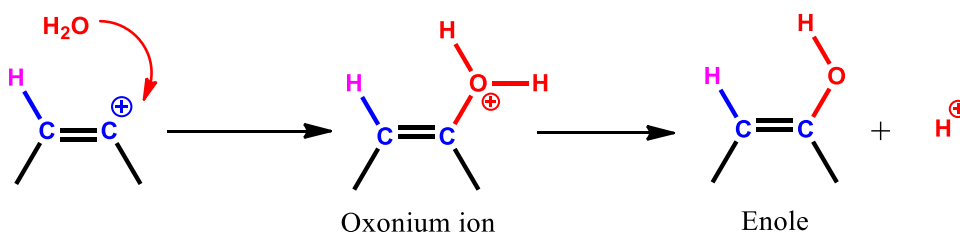
Step one

The first step is a slow process whereby a hydrogen proton adds to an sp carbon atom, which results in a vinyl carbocation intermediate.

Vinyl carbocation

Second step

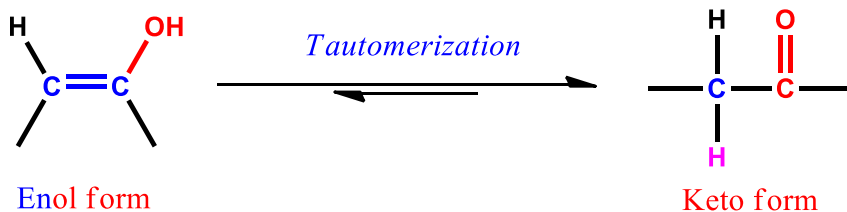
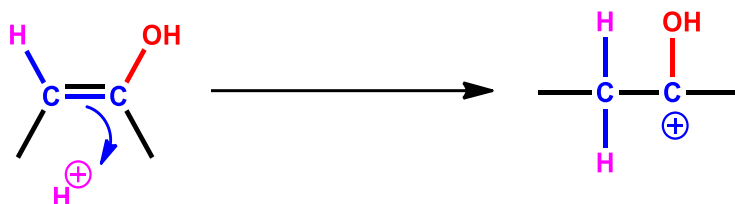
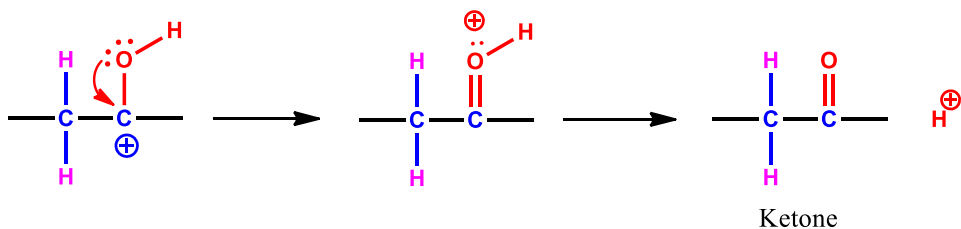
In the next step, a water molecule would attack the carbocation to produce an oxonium ion, which then gets deprotonated and an enol forms.

Oxonium ion

Enole

Enol is a term used in organic chemistry to describe compounds that contain a hydroxy group and a double bond. The suffix –en refers to the double bond while –ol refers to the hydroxy group.

Step three

Enol compounds have weak double bond, which makes them unstable compared to carbonyl double bond. As a result, enols are generally not observed as reaction products in acid catalyzed hydration of alkynes and they rapidly tautomerize into a more stable isomer known as keto -tautomer. This type of functional group conversion is called *keto-enol* tautomerisation.

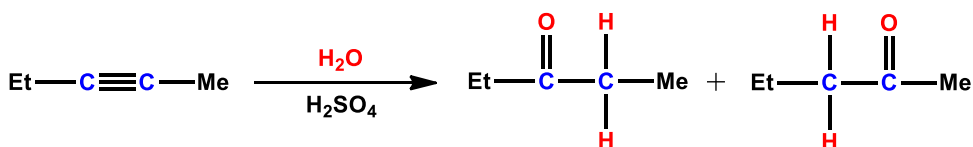
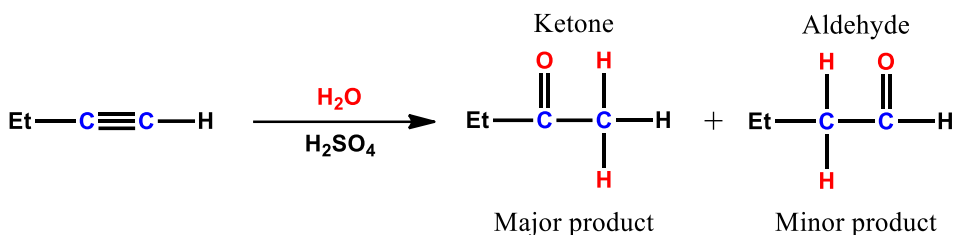
Enol form ⇌ (Tautomerization) Keto form

Under acidic condition, the double bound of enol abstracts one hydrogen proton from a proton donor "catalyst or solvent", which leads to the formation of a carbocation on the carbon atom attached to the hydroxy group.

Later on, one electron lone pair of oxygen would migrate towards the carbocation resulting in a protonated ca rbonyl intermediate, which then gets deprotonated to give a carbonyl compound.

Ketone

In terms of regiochemistry, acid catalyzed hydration of internal alkynes gives two ketone isomers. On the other hand, terminal alkynes favor ketones over aldehydes.

➲ ***Example***

$$Et-C\equiv C-Me \xrightarrow[H_2SO_4]{H_2O} Et-CO-CH_2-Me + Et-CH_2-CO-Me$$

$$Et-C\equiv C-H \xrightarrow[H_2SO_4]{H_2O} Et-C(=O)-CH_2-H + Et-CH_2-C(=O)-H$$

Ketone — Major product; Aldehyde — Minor product

III. 4. 2. 8. Oxymercuration-Demercuration Hydration

Oxymercuration-demercuration describes the reaction in which an alkeneor alkyne reacts with a mercury salt in the presence of water. This particular reaction is typically used to avoid carbocation rearrangement observed in acid catalyzed hydration of alkenes and with terminal alkynes.

Alkenes

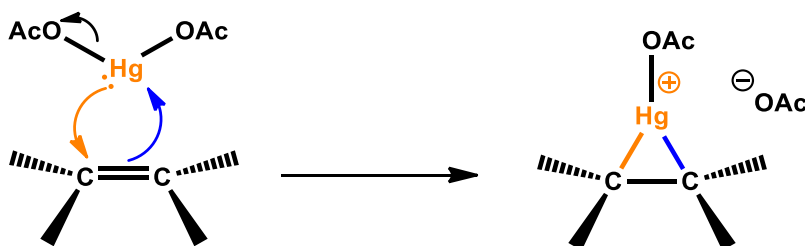
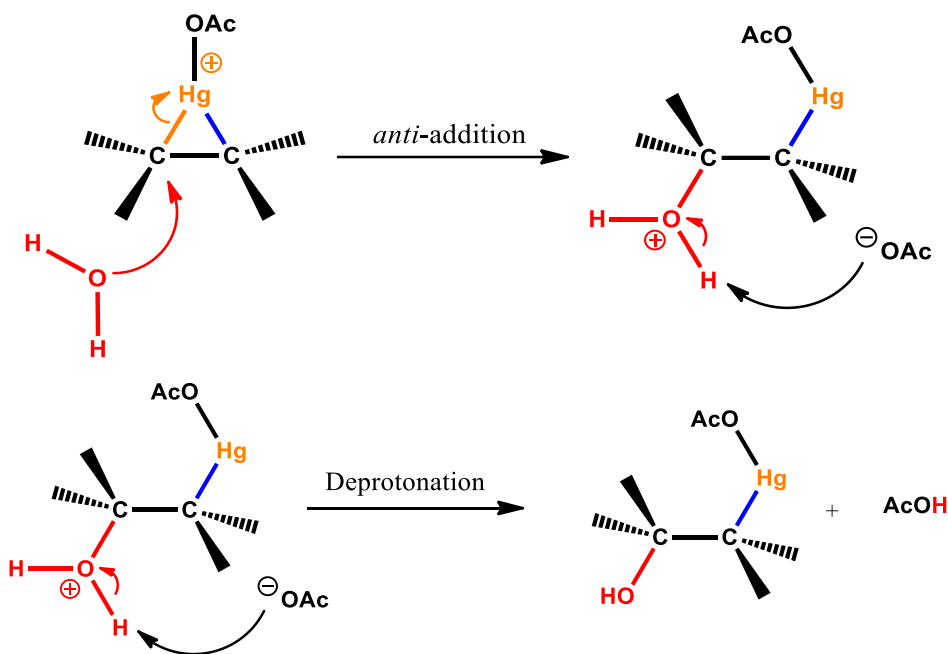
Oxymercuration-demercuration of alkenes yields the corresponding al cohols without carbocation rearrangement.

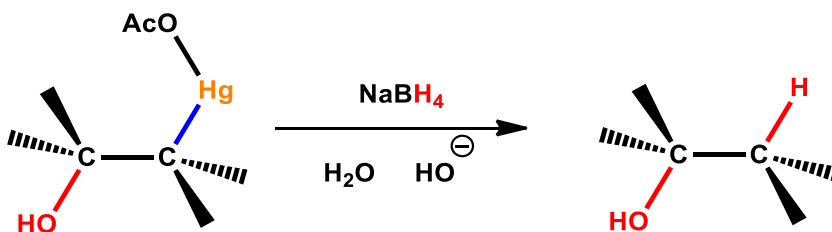
Mechanism

Oxymercuration-demercuration reaction proceeds in two steps and involves organomercury intermediate.

Oxymercuration

Initially, the double bond of the alkene attacks the mercury atom and forms a three membered cyclic organomercury intermediate.

AcO–Hg–OAc + C=C ⟶ cyclic mercurinium ion (Hg⁺–OAc bridging C–C) + $^{\ominus}$OAc

Later on, the weak nucleophile water would attack the most substituted carbon atom of the cyclic intermediate. This nucleophilic attack proceeds exclusively via *anti*-addition and leads to an oxon ium ion intermediate, which then gets deprotonated by the solvent or acetate AcO^{-} forming a hydroxy mercury intermediate.

Demercuration

The next step involves a reduction reaction whereby the mercury group gets displaced by a hydride ion. This step is carried out with $NaBH_4$ under aqueous alkali condition.

Regiochemistry and Stereochemistry

Oxymercuration-demercuration is a **highly regioselective reaction** that almost exclusively produces Markovnikov product. Moreover, the addition of the hydrogen proton and hydroxy group proceeds exclusively via *anti*-addition, which makes the reaction **regiospecific**. In terms of stereochemistry, oxymercuration - demercuration is a **non-stereoselective reaction** since it produces both possible stereoisomers.

➲ *Example*

Oxymercuration-demercuration of (E)-3-ethyl-2-methylhex-3-ene gives a racemic mixture of 3-ethyl-2-methylhexan-3-ol.

Step one

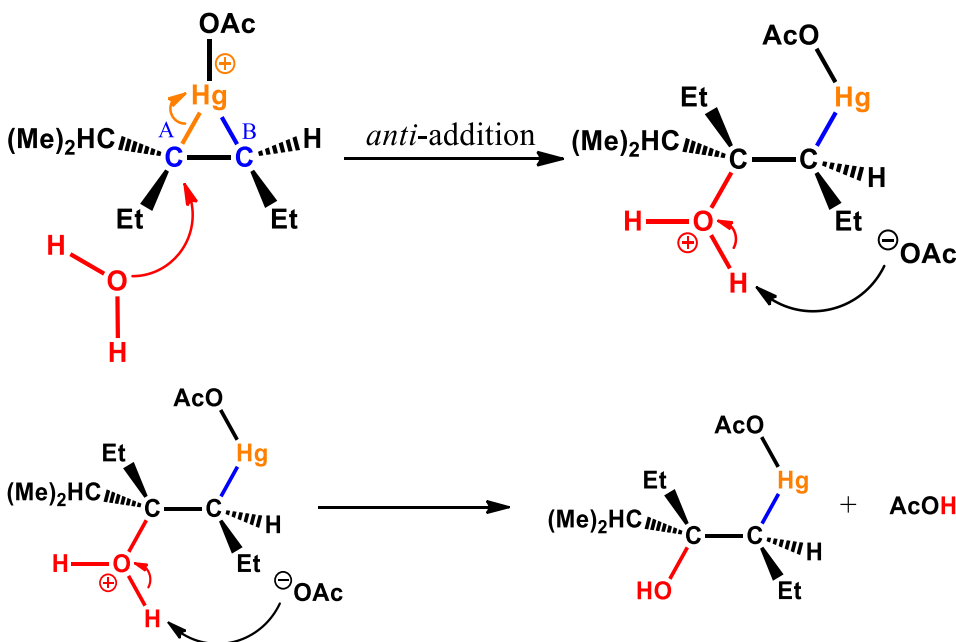
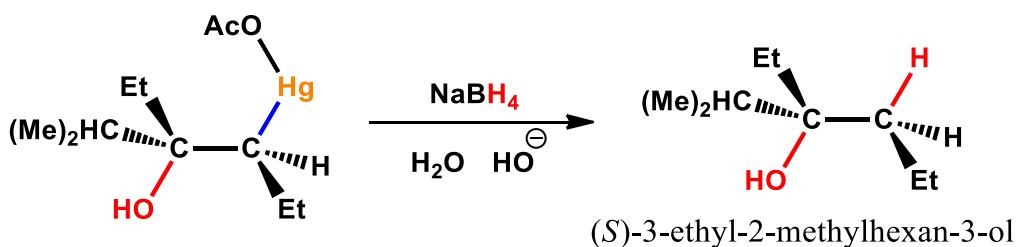
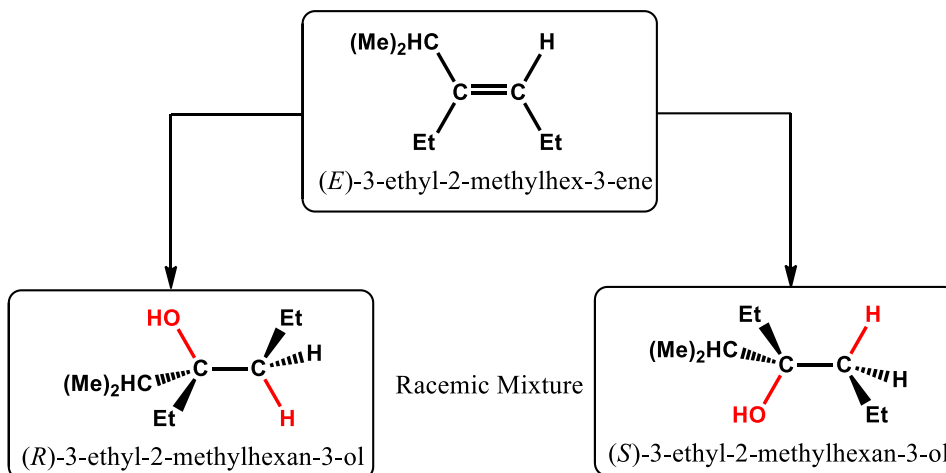
Step two

anti-addition

Step three

$NaBH_4$

H_2O $HO^{\ominus}$

(*S*)-3-ethyl-2-methylhexan-3-ol

Alkynes

Oxymercuration-demercuration of alkynes is usually performed with mercuric sulfate in aqueous sulfuric acid. Just like in acid catalyzed hydration, this reaction follows Markovnikov's rule and give ketones.

Mechanism

The first steps of the mechanism are the same as in the oxymercu ration of alkene. However, the second step does not require a reducing agent to give the corresponding enol. In this case, demercuration can be accomplished by protonation of the double bond, which subsequently leads to the elimination of the mercury and the formation of an enol, which then tautomerizes into a ketone under acidic condition.

Oxymercuration

Demercuration

III. 4. 2. 9. Hydroboration Oxidation

Hydroboration oxidation reaction is another method to synthesize alcohols from alkenes and aldehydes from alkynes. Unlike the previous reactions, hydroboration oxidation does not involve an ionic intermediate.

Alkenes

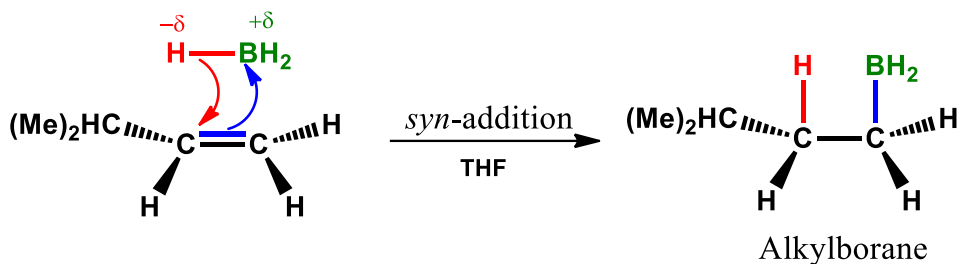
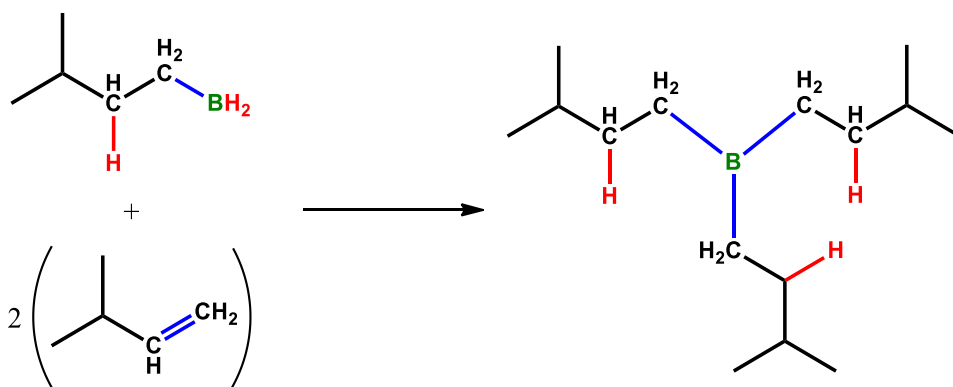
Alkenes react with hydroborane to give alkylboranes, which subsequently transform into the corresponding alcohols.

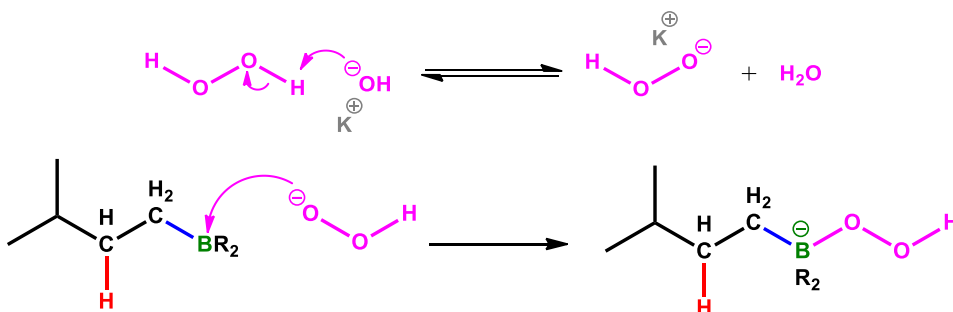
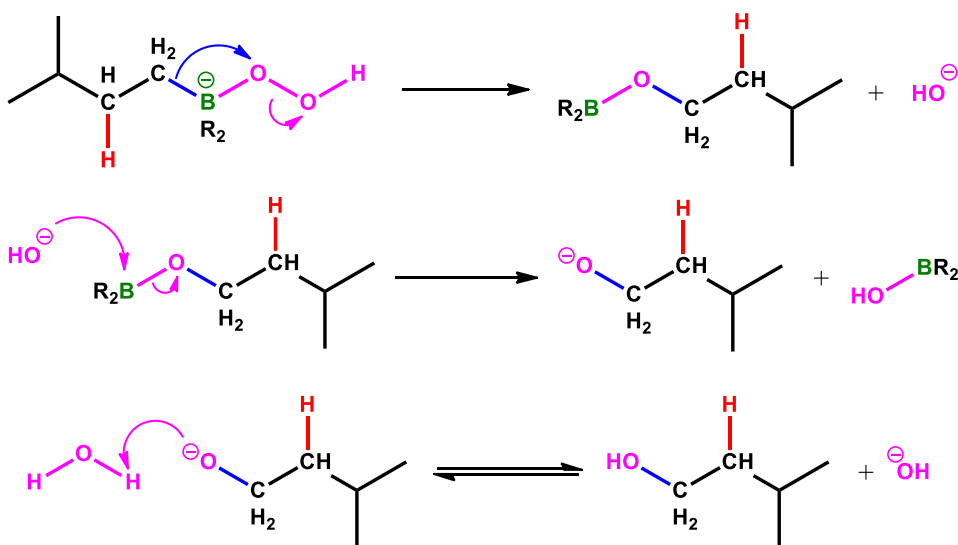
Mechanism

The mechanism of alkene hydroboration oxidation proceeds in two steps.

Step one

Initially, hydroborane adds to the double bond of the alkene through a concerted *syn*-addition, which leads to an alkylborane intermediate.

(Me)$_2$HC–CH=CH$_2$ + H–BH$_2$ $\xrightarrow[THF]{syn\text{-addition}}$ Alkylborane

In general, BH_3 adds to three alkenes molecule.

Step Two

The second step of this reaction consists in oxidizing the alkylborane intermediate under basic condition in the presence of hydrogen peroxide.

Regiochemistry and Stereochemistry

Hydroboration oxidation is a **regioselective** reaction that follows anti - Markovnikov's rule where hydrogen proton preferentially adds to the most substituted sp^2 carbon atom. Moreover, it is a **regiospecific** reaction that proceeds exclusively via *syn*-addition. In terms of stereochemistry, hydroboration oxidation is a **stereospecific** reaction where *E* and *Z* stereoisomers yield different stereoisomers. However, this reaction is **non-stereoselective** where both stereoisomers can be formed.

➲ ***Example***

Hydroboration oxidation of (*E*)-3-methylpent-2-ene yields a racemic mixture of 3-methylpentan-2-ol as major products. Similarly, when using (*Z*)-3-methylpent-2-ene, the reaction gives a racemic mixture of 3-methylpentan-2-ol. However, products obtained from *E* stereoisomer are not enantiomers of products obtained from the *Z* stereoisomer.

(*E*)-3-methylpent-2-ene

(2*S*,3*R*)
-3-methylpentan-2-ol

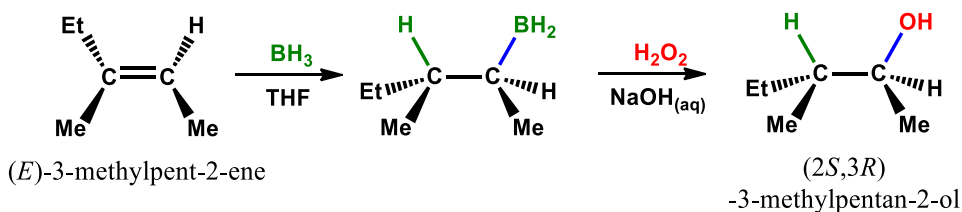
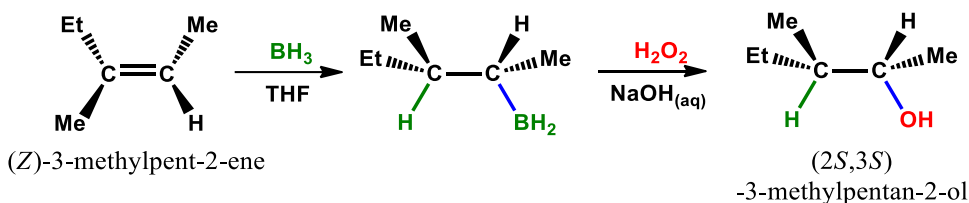
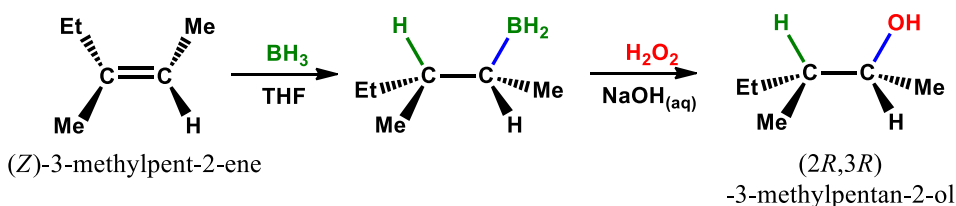
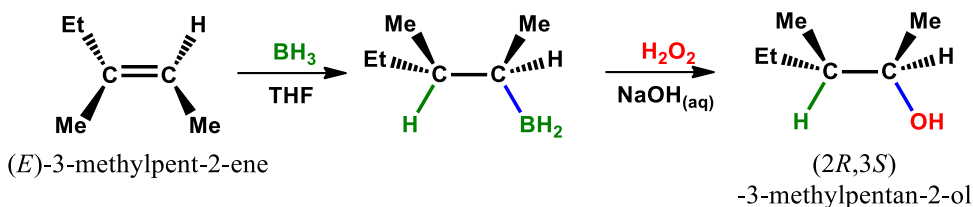
(*E*)-3-methylpent-2-ene

(2*R*,3*S*)
-3-methylpentan-2-ol

(*Z*)-3-methylpent-2-ene

(2*R*,3*R*)
-3-methylpentan-2-ol

(*Z*)-3-methylpent-2-ene

(2*S*,3*S*)
-3-methylpentan-2-ol

Alkynes

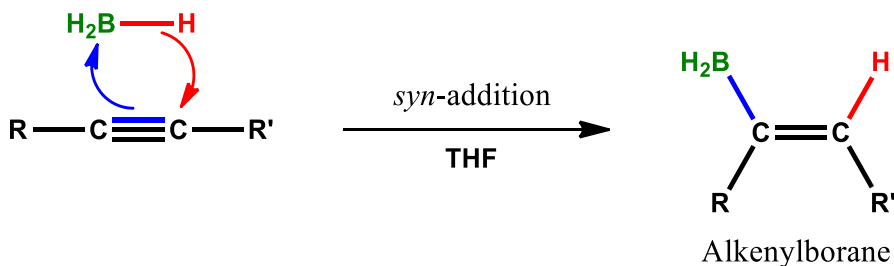
Alkynes react with borane to give enols, which then tautomerize into carbonyl compounds. Terminal alkynes give aldehydes while internal alkynes yield ketones.

Mechanism

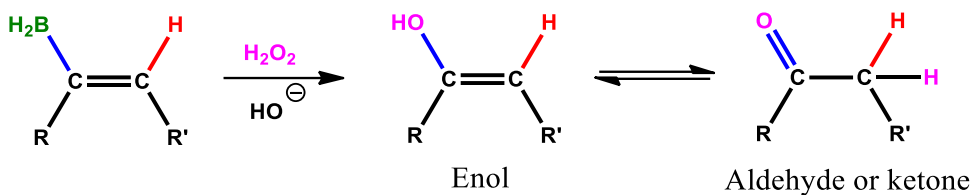
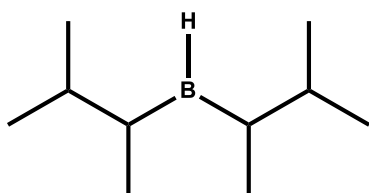
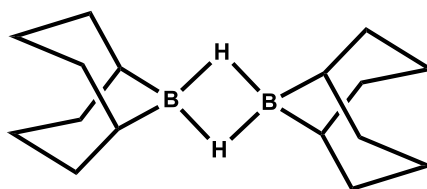
Hydroboration oxidation of alkynes follows the same process of alkenes hydroboration oxidation. Initially, BH_3 adds to the alkyne via *syn*-addition resulting in an alkenylborane intermediate.

syn-addition

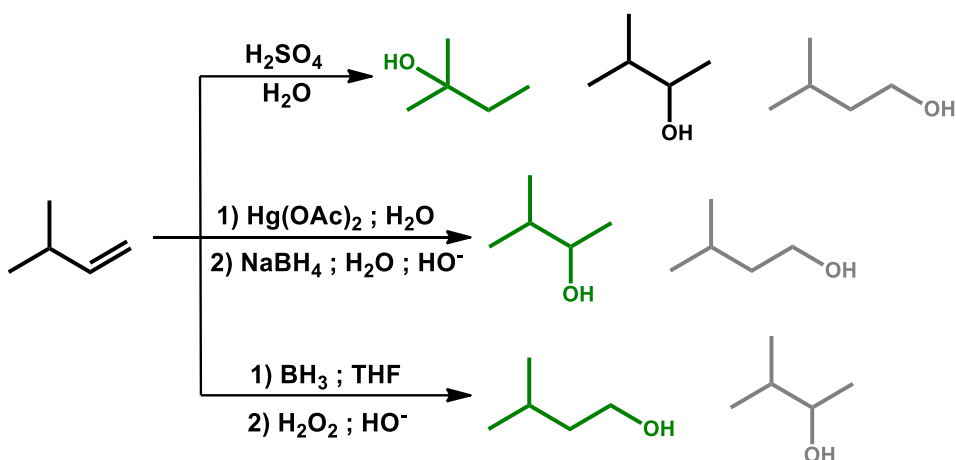
THF

Alkenylborane

Later on, this particular intermedia te oxidizes by alkaline hydrogen peroxide and yields an enol product, which will tautomerize to a ketone or aldehyde depending upon the structure of the alkyne used.

Enol

Aldehyde or ketone

In order to optimize the regioselectivity of this reaction, more sterically hindered borane compounds such as disiamyl borane or 9-BBN can be used.

bis(3-methylbutan-2-yl)borane
or
Disiamylborane

9-Borabicyclo[3.3.1]nonane
or
9-BBN

Important differences between acid catalyzed hydration, oxymercuration-demercuration, and hydroboration oxidation of alkenes.

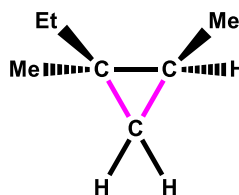
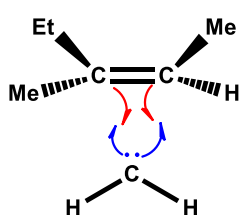
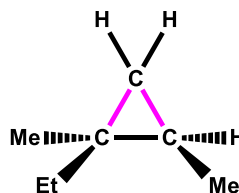
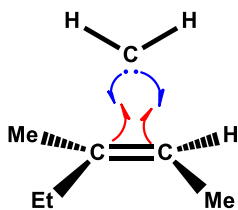
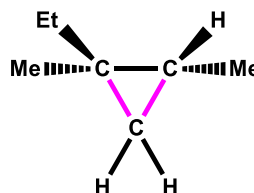
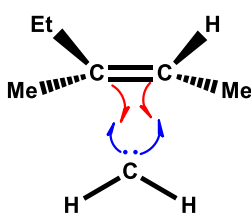
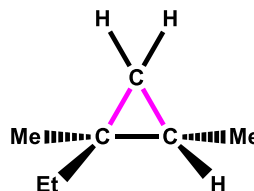
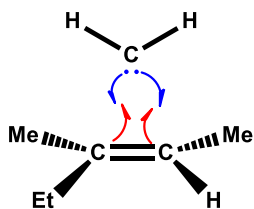
Acid Catalyzed Hydration	Oxymercuration-Demercuration Hydration	Hydroboration Hydration
Carbocation rearrangement Markovnikov's product	No carbocation rearrangement Markovnikov's product	No carbocation rearrangement Anti-Markovnikov's product

III. 4. 3. Concerted Addition Reactions

Concerted addition reactions are reactions that occur in one step whereby chemical bonds form and break simultaneously without involving any ionic intermediate.

III. 4. 3. 1. Addition of Carbenes

Alkenes react with carbene species to form three -membered cyclic compounds. This reaction can follow different mechanism depending upon the nature of carbene involved. Singlet carbenes add to the π bond through a concerted mechanism. On the other hand, addition of triplet carbenes to the π bond is not concerted.

Singlet Carbenes

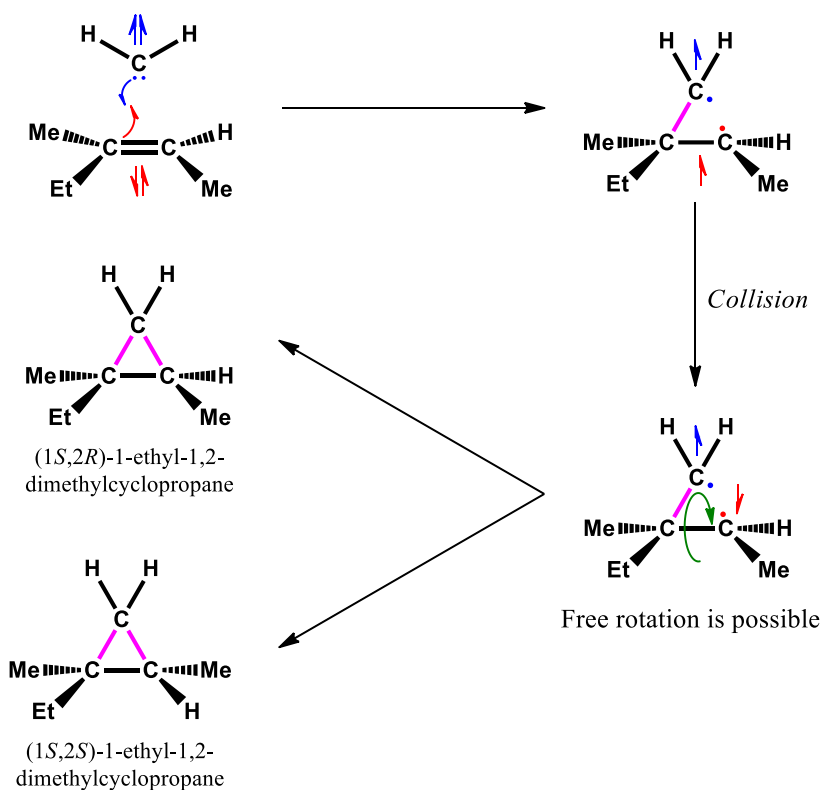
Singlet carbenes are spin-paired non-ionic reactive species that exhibit both electrophilic and nucleophilic characters. When a singlet carbene reacts with an alkene, each sp^2 carbon atom of the π bond forms a covalent bond with the carbene by providing a single electron. In terms of stereochemistry, addition of singlet carbenes to asymmetrical alkenes is a **stereospecific** reaction but **not stereoselective**.

Triplet Carbenes

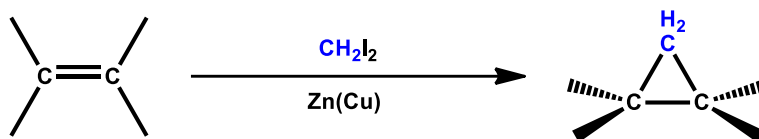
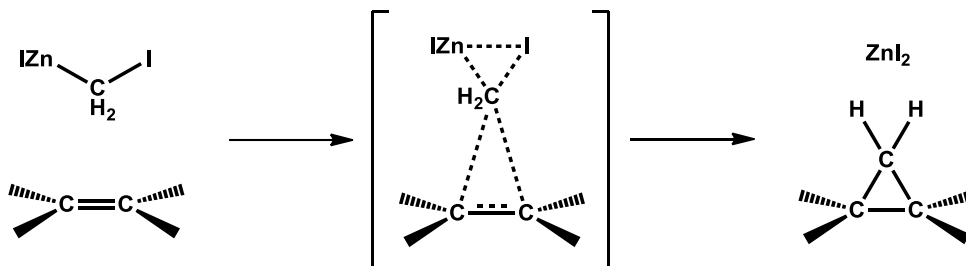
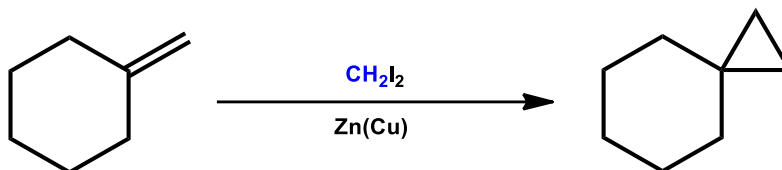
Triplet carbenes have two unpaired electrons of identical spin. Unlike singlet carbenes, reactions involving triplet carbenes are **non-stereospecific**. In this case, the triplet carbene does not add to the π bond in a concerted manner but rather passes through three steps. At first, the π bond cleaves homolytically and forms a covalent bond with the triplet carbene. In this case, the opposite spins overlap and form a covalent bond leaving two carbon free radicals of identical spins. At this point, covalent bond between these two radicals is not possible. The next step involves a collision where the identical spins of carbon radicals are converted into opposite ones, which allows them to form a covalent bond in the final step.

Collision

(1*S*,2*R*)-1-ethyl-1,2-dimethylcyclopropane

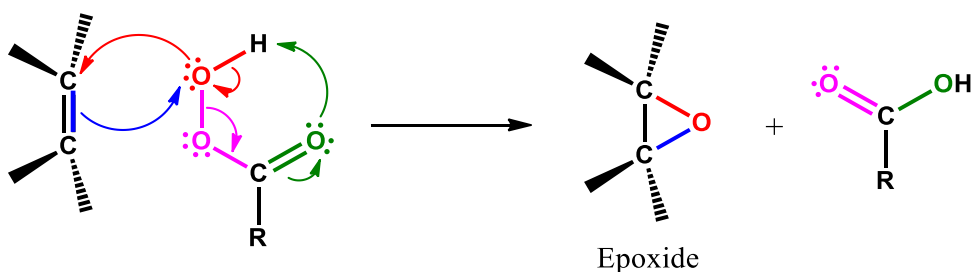
Free rotation is possible

(1*S*,2*S*)-1-ethyl-1,2-dimethylcyclopropane

Simmons-Smith Reaction

Simmons-Smith reaction consists in forming cyclopropanes from alkenes. This particular reaction involves an organo-zinc carbenoid, which consists in generating a methylene free radical that simultaneously adds to both sp^2 carbons.

Simmons-Smith reaction is more favorable procedure to synthesis cyclopropanes than using regular carbene species. It is carried out with zinc -copper couple and diiodomethane, which react and produce the reactive organozinc species.

Moreover, Simmons-Smith reaction is also suitable for the synthesis of spirocyclic compounds.

III. 4. 3. 2. Epoxidation

Epoxidation of alkenes is the reaction whereby one oxygen atom adds to both sp^2 carbon atoms of the π bond resulting in a three-membered heterocyclic ring known as epoxide, or oxirane according to heterocyclic compound nomenclature. This particular reaction occurs when treating an alkene with a peroxy acid, also known as peracid, such as *m*–chloroperbenzoic acid (mCPBA). Moreover, epoxidation is one of the most important reactions of alkenes since many organic syntheses involve epoxide intermediates.

Mechanism

Epoxidation of alkenes is a concerted reaction that occurs in one step where each carbon of the double bond forms a covalent bond with the same oxygen atom as the π bond breaks.

Epoxide

Regiochemistry and Stereochemistry

Epoxidation of asymmetrical alkenes is a **non-stereoselective** reaction that yields a racemic mixture of epoxides. The reason behind this is that the oxygen can add to either sides of the π bond. Nevertheless, this reaction is **stereospecific** where E and Z diastereoisomers give different racemic mixtures of epoxides.

➲ ***Example***

Epoxidation of (*E*)-3-methylpent-2-ene give two enantiomers that differs from enantiomers obtained from (*Z*)-3-methylpent-2-ene.

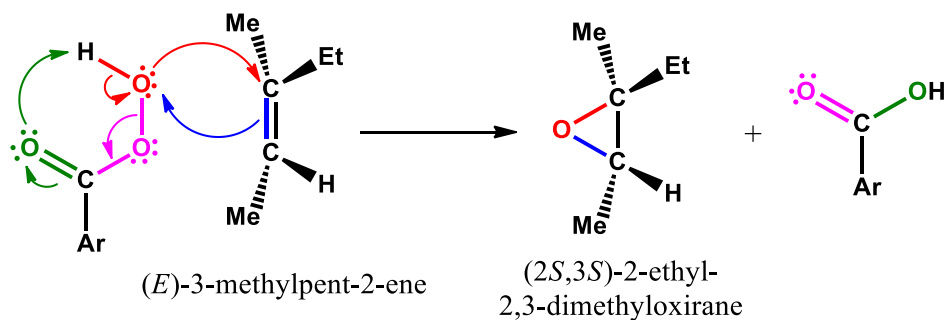
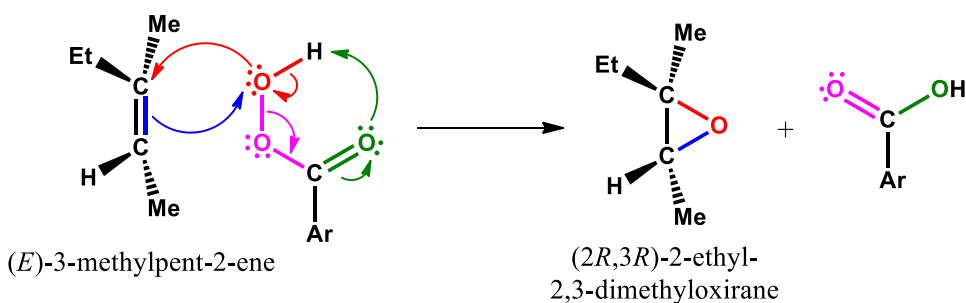
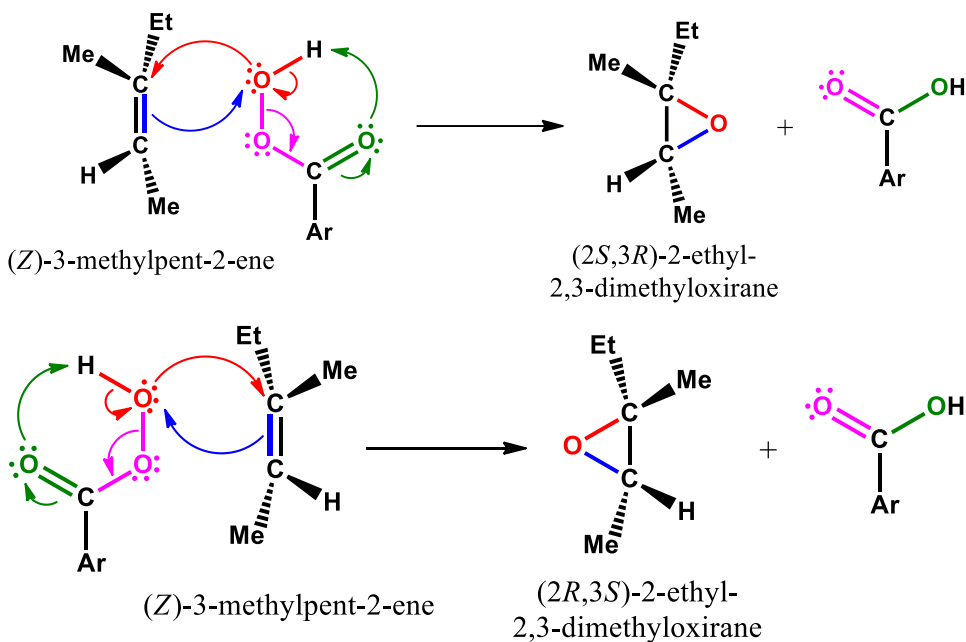
(*E*)-3-methylpent-2-ene → (2*R*,3*R*)-2-ethyl-2,3-dimethyloxirane

(*E*)-3-methylpent-2-ene → (2*S*,3*S*)-2-ethyl-2,3-dimethyloxirane

(*Z*)-3-methylpent-2-ene

(2*S*,3*R*)-2-ethyl-2,3-dimethyloxirane

(*Z*)-3-methylpent-2-ene

(2*R*,3*S*)-2-ethyl-2,3-dimethyloxirane

III. 4. 3. 3. Hydrogenations Reaction

Hydrogenation of unsaturated hydrocarbons is a reduction reaction whereby two or four hydrogen atoms add to the substrate as the π bonds break. This reaction is carried out with gaseous hydrogen and a transition metal catalyst such as Pt, Pd, Ni, and Rh. Catalytic hydrogenation of alkenes gives fully saturated hydrocarbons. . For alkynes, however, the reaction may proceed all the way to the corresponding alkanes or stops at partial hydrogenation, which gives the corresponding alkenes depending upon reaction conditions.

Alkenes Hydrogenation

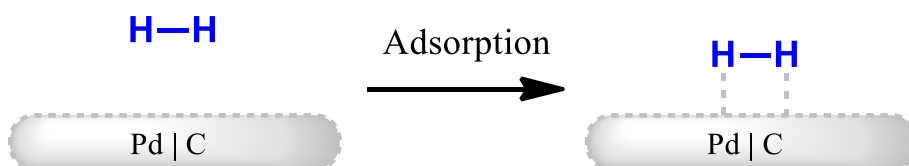
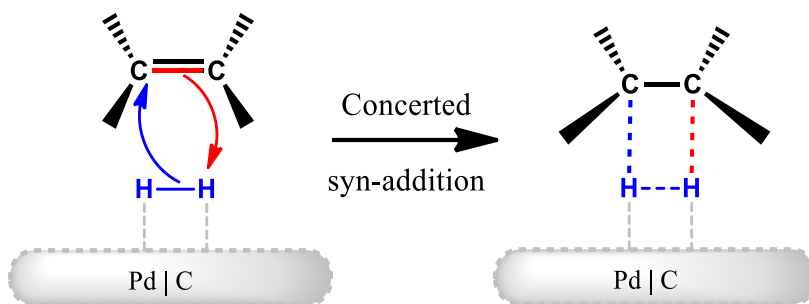
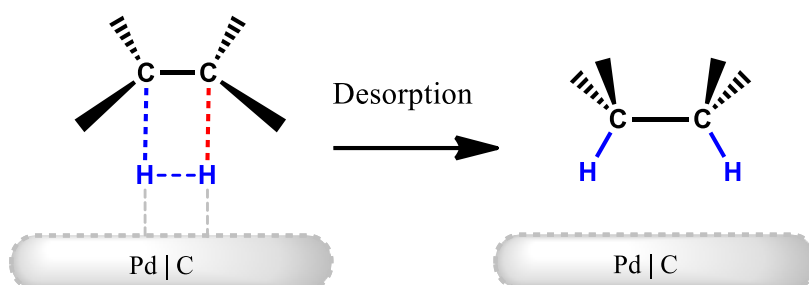
Catalytic hydrohalogenation of alkenes is a concerted reaction whereby two hydrogen atoms add to vicinal sp^2 carbons. This re action starts by introducing gaseous hydrogen to a transition metal catalyst under high pressure, which leads to the adsorption of hydrogen molecules onto the surface of the catalyst.

H—H

Pd | C

Adsorption

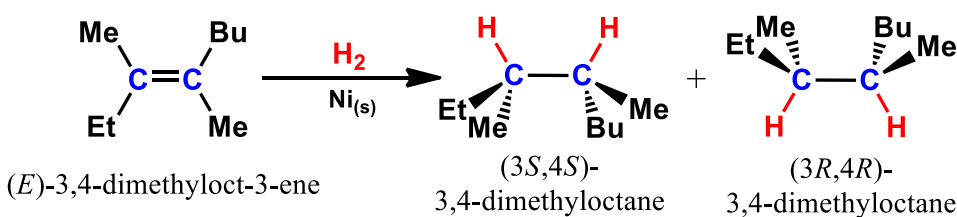
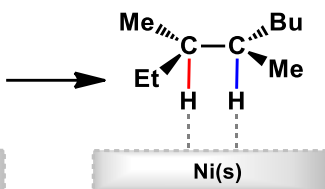
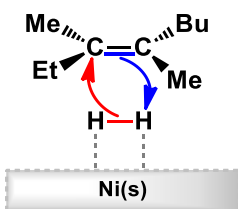
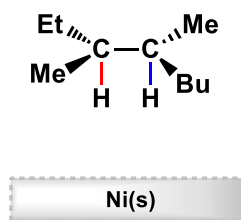
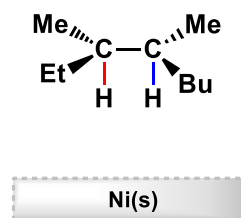
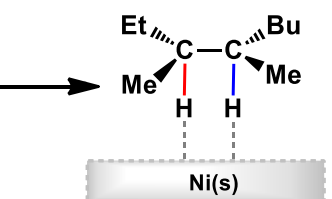
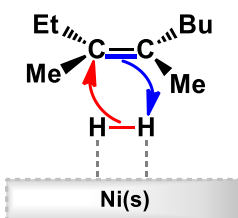
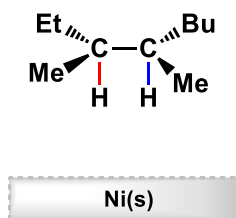
H—H

Pd | C

Later on, alkene molecule would appro ach the surface on which hydrogen atoms are attached. At this point, new C–H covalent bonds form as the π bond breaks.

Finally, the adduct leaves the surface of the catalyst allowing another h ydrogen molecule to be adsorbed.

Regiochemistry and Stereochemistry

Catalytic hydrohalogenation is a **regiospecific reaction** that proceeds exclusively via *syn*-addition, and a **stereospecific reaction** that produces specific stereoisomers from specific stereoisomers. Moreover, since hydrogenation uses a symmetrical reagent, no regioselectivity is observed and therefore it is a **non-regioselective reaction**.

➲ ***Example***

Catalyzed hydrogenation of (*E*)-3,4-dimethyloct-3-ene gives two enantiomers.

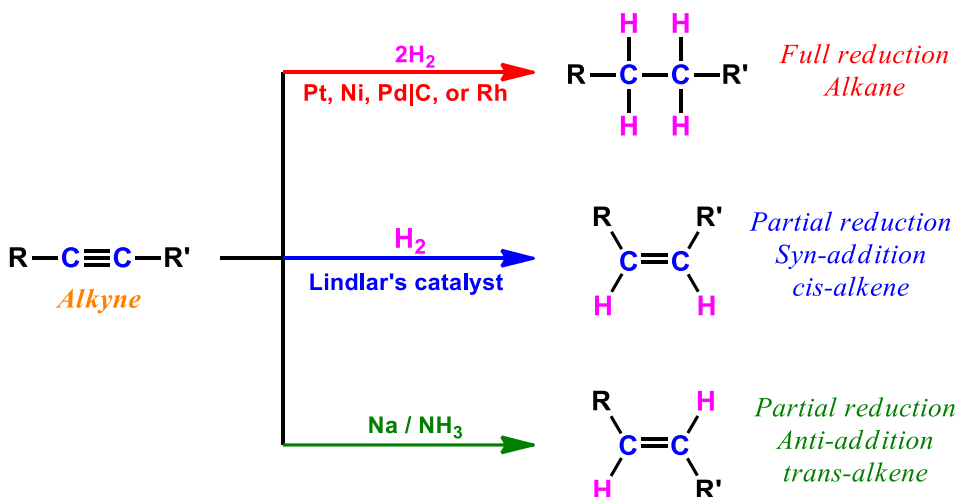
Me, Bu, Et, Me — C=C — H_2 / $Ni_{(s)}$ → H, H, Et, Me, Bu, Me + Et, Me, Bu, Me, H, H

(*E*)-3,4-dimethyloct-3-ene — (3*S*,4*S*)-3,4-dimethyloctane + (3*R*,4*R*)-3,4-dimethyloctane

Similarly, (*Z*)-3,4-dimethyloct-3-ene yields two enantiomers that differ from the enantiomers obtained from (*E*)-3,4-dimethyloct-3-ene.

Alkynes Hydrohalogenation

Unlike alkenes, hydrogenation of alkynes can be controlled to get *cis*-alkenes, or fully saturated hydrocarbon “alkanes” depending upon reagent used. *trans*-alkenes can be obtained via another procedure that involves alkali metal in the presence of liquid ammonia. This particular reaction is not concerted and it proceeds in two steps.

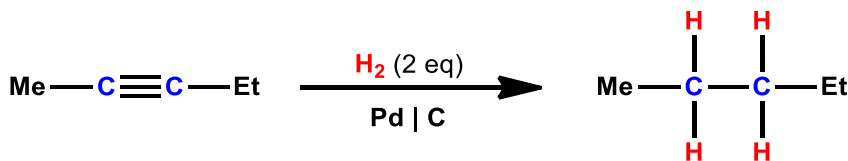
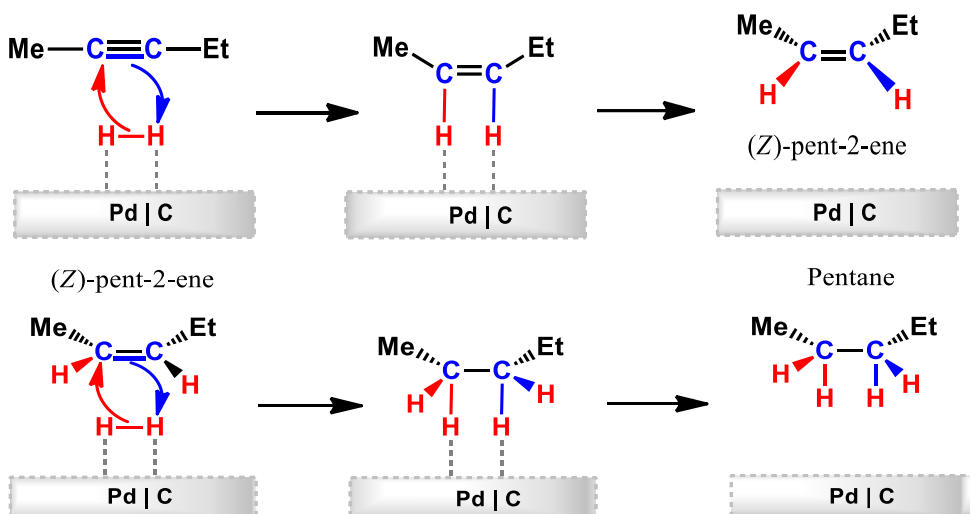
R—C≡C—R' (*Alkyne*)

$2H_2$ / Pt, Ni, Pd|C, or Rh → R—CH₂—CH₂—R' *Full reduction* *Alkane*

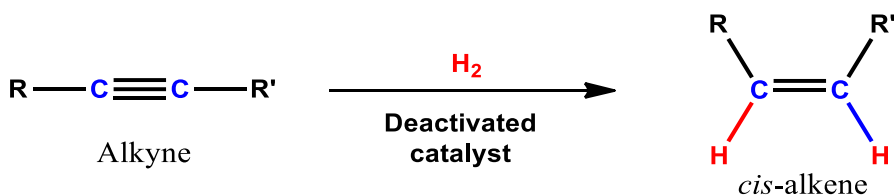
H_2 / Lindlar's catalyst → RHC=CHR' *Partial reduction* *Syn-addition* *cis-alkene*

Na / NH_3 → RHC=CHR' *Partial reduction* *Anti-addition* *trans-alkene*

From alkynes to alkanes

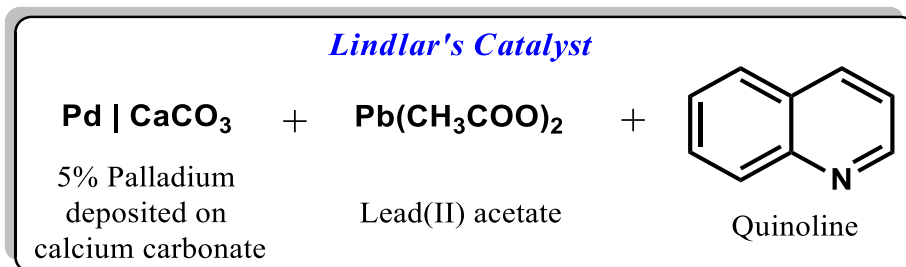
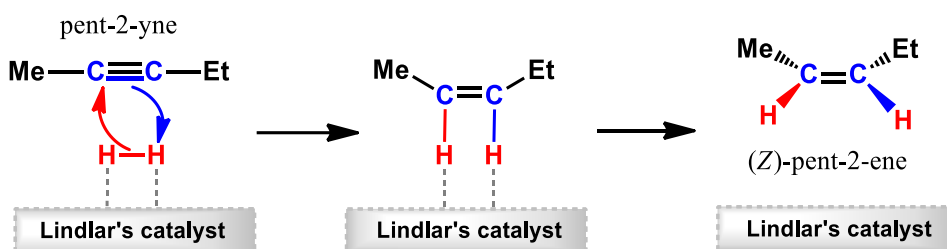
Using a transition metal catalyst such as Pt, Pd, Ni, or Rh, alkynes can be directly reduced to the corresponding alkanes.

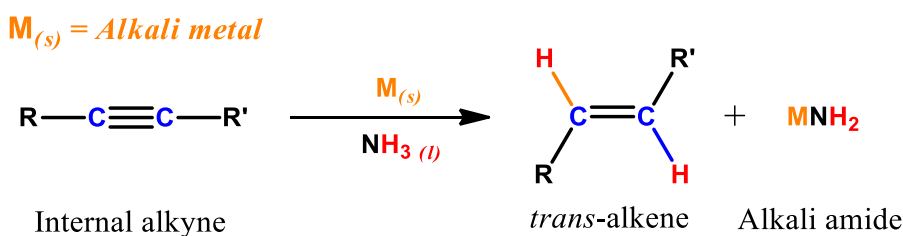
Me—C≡C—Et —[H_2 (2 eq), Pd | C]→ Me—CH₂—CH₂—Et

This process proceeds in two fast steps. Initially, two hydrogen atoms add to two sp carbon atoms via a *syn*-addition resulting in a *cis*-alkene. This particular *cis*-alkene cannot be isolated from the reaction media because the catalyst used is highly active and further hydrogenation immediately takes place to give the corresponding alkane. In this case, the stereochemistry is not important because the reduced sp carbon atoms will acquire two additional hydrogen atoms and therefore they become achiral carbons.

From alkynes to *cis*-alkenes

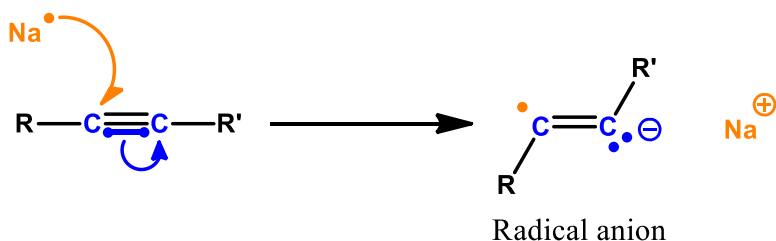
Named after its inventor, the British-Swiss chemist *Herbert Lindlar–Wilson*, Lindlar's catalyst is a poisoned "deactivated" catalyst used for catalytic hydrogenation of alkynes in order to obtain the corresponding *cis*–alkenes without further reduction to the corresponding alkane.

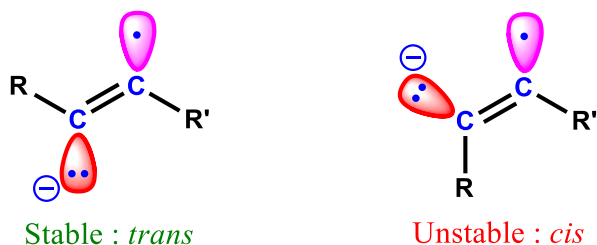
R—C≡C—R' Alkyne $\xrightarrow[\text{Deactivated catalyst}]{H_2}$ *cis*-alkene

Even though Lindlar's catalyst is commercially available, it can be easily prepared in the laboratory through reduction of palladium(II) chloride $PdCl_2$ in semi-liquid calcium carbonate $CaCO_3$ followed by the poising of the resulting mixture with a suitable catalyst poison such as lead(II) acetate $Pb(CH_3COO)_2$, or lead(II) oxide PdO, and quinoline. In general, palladium accounts for only 5% of the total weight.

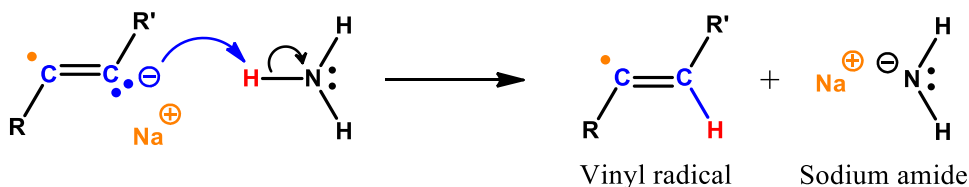
Lindlar's Catalyst

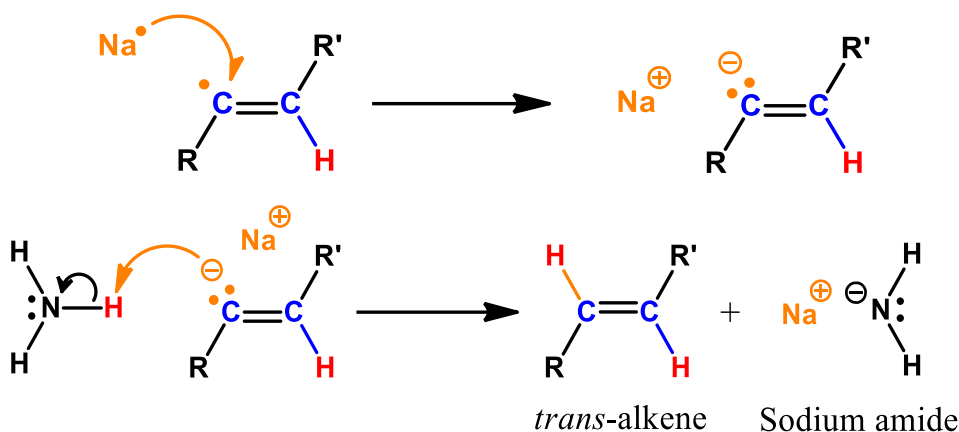
Pd | $CaCO_3$	+	$Pb(CH_3COO)_2$	+	Quinoline
5% Palladium deposited on calcium carbonate		Lead(II) acetate		Quinoline

Just like the typical catalytic hydrogenation of unsaturated hydrocarbons, catalytic hydrogenation of alkynes with Lindlar's c atalyst consists in adding two hydrogen atoms to two sp carbon atoms via *syn*-addition, which leads to the formation of the corresponding *cis*–alkenes. In this case, Lindlar catalyst does not reactive enough for further hydrogenation of the *cis*–alkenes formed. The reason behind this is that the lead present in Lindlar's catalyst reduce the absorption of dihydrogen gas, while quinoline prevents the formation of unwanted byproducts.

From alkynes to *trans*-alkenes

Obtaining *trans*-alkenes from alkynes requires specific reagents so the addition of hydrogen atoms proceeds via the *anti*-addition. This reaction is **not concerted** and it is carried out with an alkali metal such as sodium, or lithium, which serves as an electron source, in liquid ammonia as hydrogen atoms source.

The reaction proceeds in two four steps that involve ionic intermediates. Initially, the alkali me tal, in this case sodium, gives one electron from its valence shell to one sp carbon atom while one π bond breaks resulting in the formation of a negative charge on the other sp carbon atom. At this point, a radical anion and a cationic sodium form.

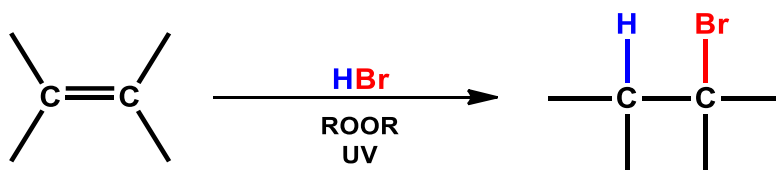
Radical anion

This particular step is what determine the stereochemistry of the corresponding *trans*–alkene. Since each carbon atom is attached to one substituent, each substituent will point as far as possible from the other substituent in order to minimize the steric hindrance. Similarly, the atomic orbital of the negative charge and the carbene will also align in an anti-periplanar way, which reduces the electronic repulsion between the electronic charges. As a result, the radical anion must have a *trans* configuration.

Stable : *trans* Unstable : *cis*

The next step is an acid -base interaction whereby the radical anion acquire one hydrogen atom. At this point, ammonia acts as an acid by providing the radical anion with one hydrogen proton, which adds to the carbon atom that bears the negative charge resulting in a vinyl radical.

Vinyl radical Sodium amide

Later on, the vinyl radical receives one electron from sodium resulting is an anionic intermediate, which then abstracts a hydrogen proton from ammonia to give the corresponding *trans*- alkene.

trans-alkene Sodium amide

III. 4. 4. Free-radical Addition Reaction

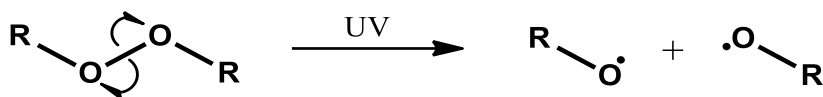
Alkenes undergo free radical addition with hydrogen bromide in the presence of an organic peroxide and yield alkyl bromides.

HBr
ROOR
UV

Mechanism

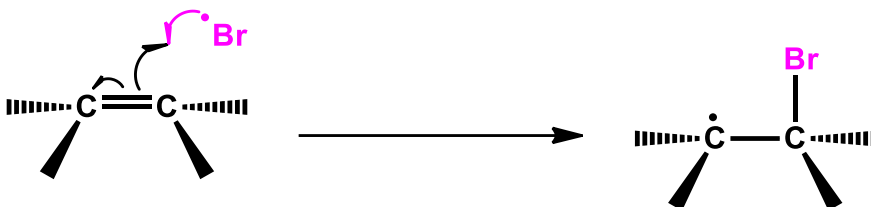
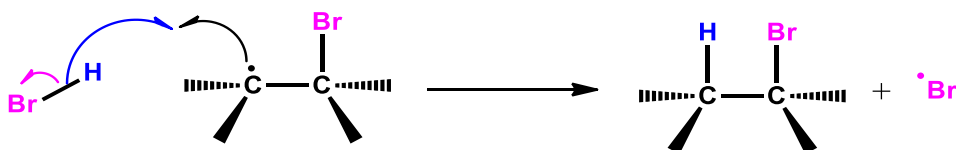
Free radical hydrobromination of alkenes is a chain reaction that proceeds in three steps.

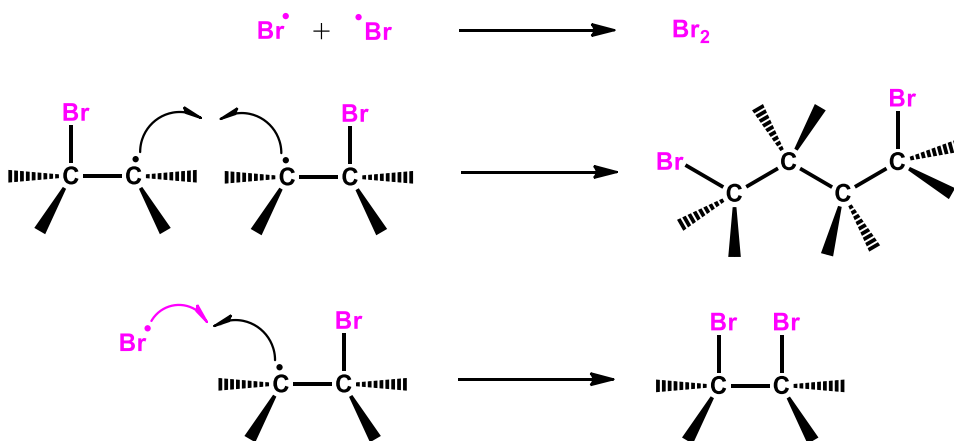
Initiation

The reaction is initiated by generating free radicals from the organic peroxide under influence of UV light or heat. At this point, the weak peroxy bond breaks homolytically leading to the formation of two alkoxy free radicals.

UV

Later on, alkoxy free radicals would abstract hydrogen atom from hydrogen bromide resulting in the formation of an alcohol and bromine free radical.

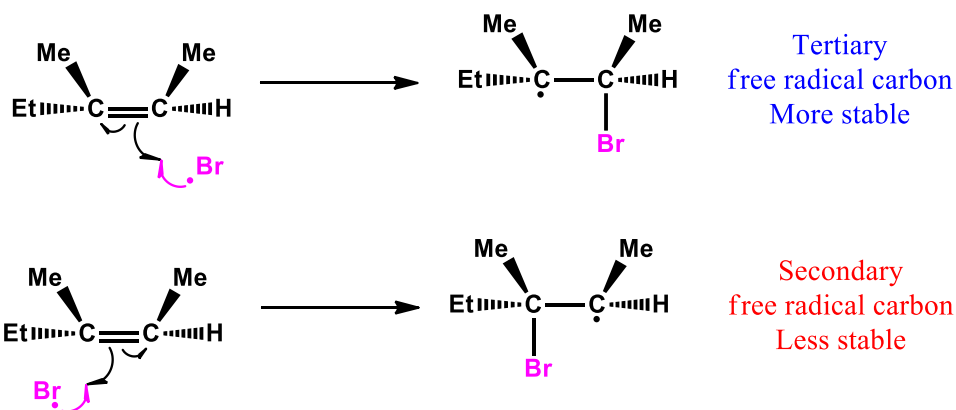
Propagation

Propagation step is a repeated process where free radicals react with neutral molecules forming new covalent bonds. At this point, bromine free radical adds to the alkene double bond, which leads to an alkyl bromide free radical intermediate. In this case, the π bond is homolytically cleaved.

In the next step, the alkyl bromide radical would abstract a hydrogen atom from hydrogen bromide forming, as a result, a bromoalkane.

Termination

Termination step is the process in which free radicals combine forming neutral compounds. At this stage, bromine free radicals may react with another bromine free radical and produce dibromine Molecule. Moreover, alkyl bromide free radicals can also undergo further bromination where they react with another bromine free radical. Another possible reaction can occur between two alkyl bromide radicals, which results in a dibromoalkane with a longer carbon chain. Nevertheless, these products are usually observed at very low rate as side products.

Regiochemistry and Stereochemistry

Free radical hydrobromination of asymmetrical alkenes is a **regioselective** reaction that follows anti-Markovnikov's rule where bromine adds to the least substituted sp^2 carbon atom. This happens because in this case, bromine adds to the π bonds before hydrogen atom, which results in an alkyl bromide radical. Since free radical carbons follow the same order of carbocation stability, bromine free radical preferentially adds to the least substituted sp^2 carbon atom in order to generate a more stable alkyl bromide radical. Nevertheless, it is important to know that only bromine follows *anti*-Markovnikov's rule due to its higher selectivity compared to other halogens.

Tertiary
free radical carbon
More stable

Secondary
free radical carbon
Less stable

In term of stereochemistry, this reaction is **non-stereoselective** because the addition of hydrogen and bromine can proceeds via *syn*-addition and *anti*-addition, which gives rise to the formation of two stereoisomers.

(2*R*,3*S*)-2-bromo-3-methylpentane

(2*R*,3*R*)-2-bromo-3-methylpentane

(2*S*,3*S*)-2-bromo-3-methylpentane

(2*S*,3*R*)-2-bromo-3-methylpentane

Moreover, whether the alkene has E configuration or Z, the reaction would yield the same stereoisomers since free rotation around σ bond is not restricted. As a result, free radical hydrobromination is a **non-stereospecific** reaction.

Et
Me
C
C
Me
H
(Z)-3-methylpent-2-ene
Et
H
C
C
Me
Me
(E)-3-methylpent-2-ene
HBr
Peroxide
Me
Br
Et
C
C
H
H
Me
(2S,3S)-2-bromo-3-methylpentane
H
Me
Et
C
C
H
Me
Br
(2R,3R)-2-bromo-3-methylpentane
H
Br
Et
C
C
H
Me
Me
(2S,3R)-2-bromo-3-methylpentane
Me
Me
Et
C
C
H
H
Br
(2R,3S)-2-bromo-3-methylpentane
Enantiomers
Enantiomers

III. 5. Oxidation Reactions

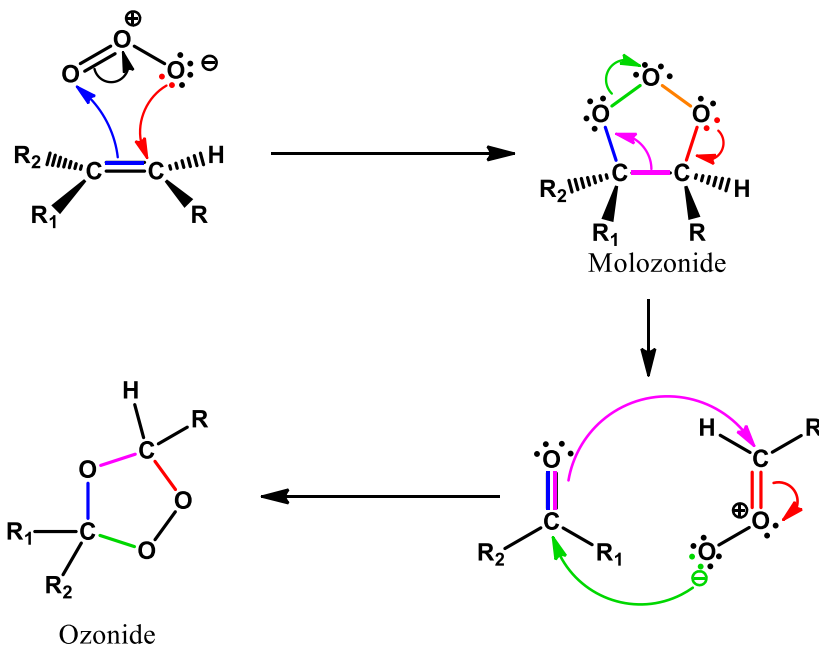
III. 5. 1. Alkenes

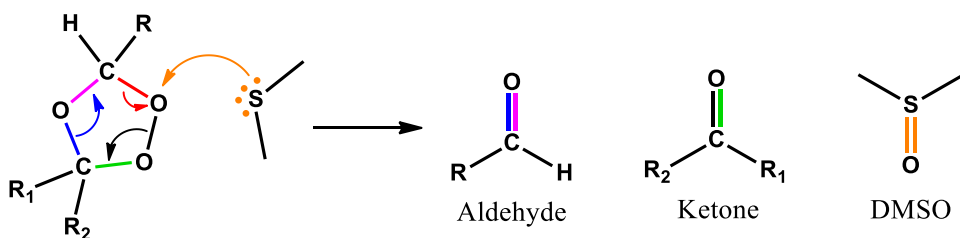
III. 5. 1. 1. Ozonolysis

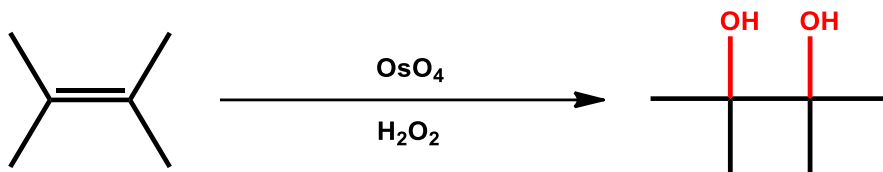
Alkenes ozonolysis describes the reaction whereby alkenes oxidize in the presence of ozone to give ketones and aldehydes. This reaction involves carbon -carbon double bond cleavage and hence, it is often called oxidative cleavage reaction.

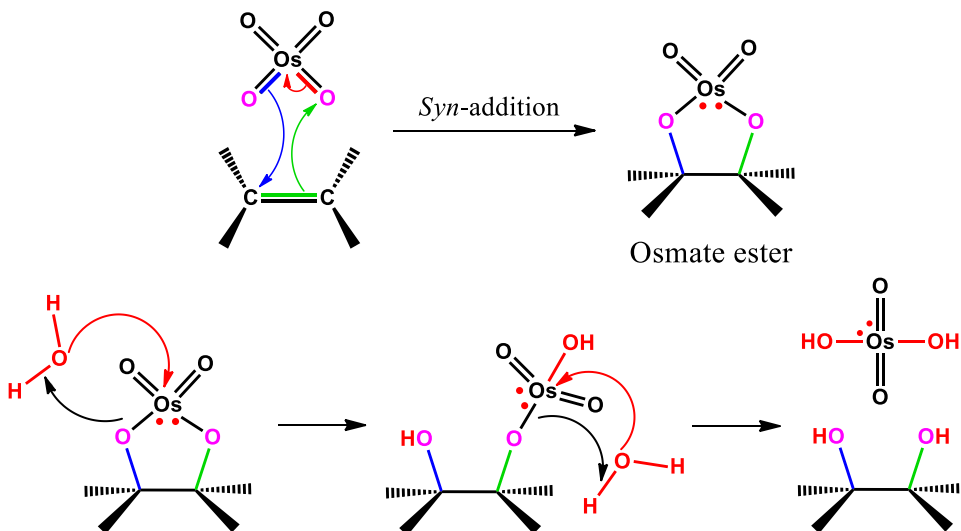
Mechanism

Oxidation of alkenes with ozone starts with the concerted addition of ozone to the π bond resulting in a molozonide intermediate. This particular intermediate would then collapse and rearrange to form a more stabilized intermediate known as ozonide.

Molozonide

Ozonide

In the last step, DMS would attack one of the ozonide's oxygen atoms, which forces the cyclic intermediate to collapse and forms the final products that might be aldehydes and/or ketones depending upon substrate structure.

III. 5. 1. 2. Oxidation with Osmium tetroxide

Dihydroxylation of alkenes with osmium tetroxide OsO_4 is an oxidation reaction whereby two hydroxy groups add to the double bond, which leads to the formation of *cis*-diols. This reaction is usually carried out with a catalytic amount of osmium tetroxide in the presence of another oxidizing agent such as hydrogen peroxide H_2O_2, tertiary amine oxides $R_3N^+O^-$, and NMO, which serves in regenerating osmium tetroxide after it gets reduced to dihydroxydioxoosmium.

Mechanism

Oxidation of alkenes with osmium tetroxide proceeds in two steps. At first, osmium tetroxide adds to the π bond in concerted manner to form osmate ester, which then collapses into a *cis*-diol upon hydrolysis workup.

Regiochemistry and Stereochemistry

Oxidation of asymmetrical alkenes with osmium tetroxide is a **regiospecific** reaction that proceeds exclusively via*syn*-addition. Moreover, because the addition of both hydroxy groups can occur on either sides of the double bond, two potential stereoisomers can be obtained, which makes this reaction **non-stereoselective**. Nevertheless, Oxidation of asymmetrical alkenes with osmium tetroxide is a **stereospecific** reaction where E and Z diastereoisomers yield different glycol stereoisomers.

➲ ***Example***

H_2O

(*E*)-3-methylpent-2-ene

(*2*S,3S)-3-methylpentane-2,3-diol

(*E*)-3-methylpent-2-ene

H_2O

(2*R*,3*R*)-3-methylpentane-2,3-diol

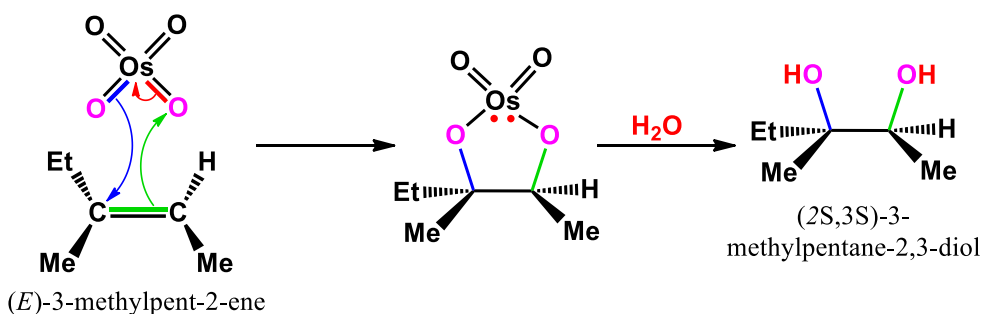
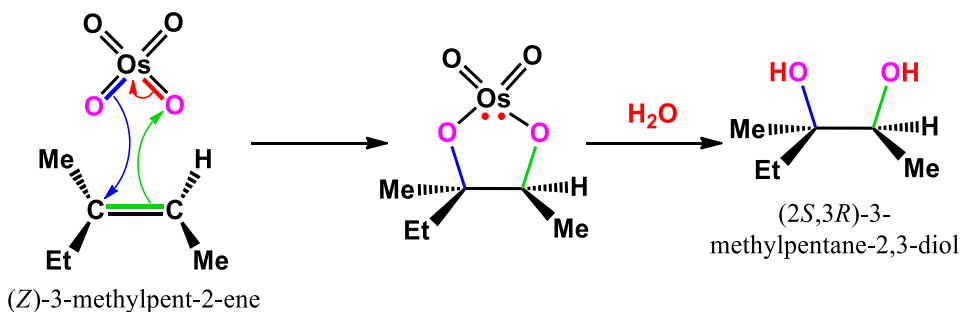
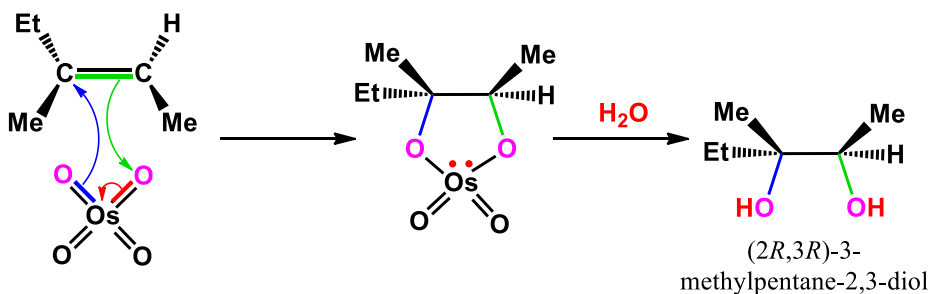
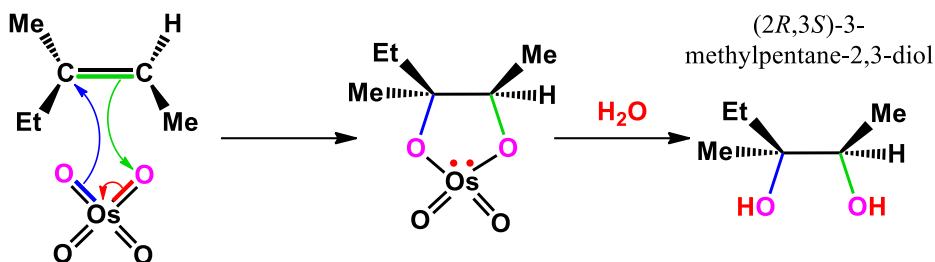
H_2O

(*Z*)-3-methylpent-2-ene

(2*S*,3*R*)-3-methylpentane-2,3-diol

(*Z*)-3-methylpent-2-ene

(2*R*,3*S*)-3-methylpentane-2,3-diol

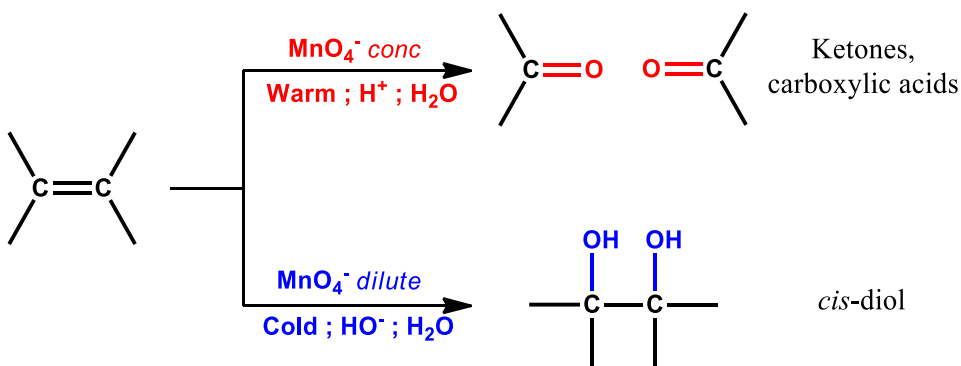
H_2O

III. 5. 1. 3. Oxidation with Potassium Permanganate

Oxidation of alkenes with potassium permanganate can follow different paths depending upon reaction conditions. Under warm acidic conditions with concentrated potassium permanganate, the double bond cleaves leading to the formation of ketones and /or carboxylic acids. On the other hand, using a dilute solution of potassium permanganate under basic cold condition s, dihydroxylation reaction would take place giving *cis*-glycols.

MnO_4^- *conc*
Warm ; H^+ ; H_2O

Ketones, carboxylic acids

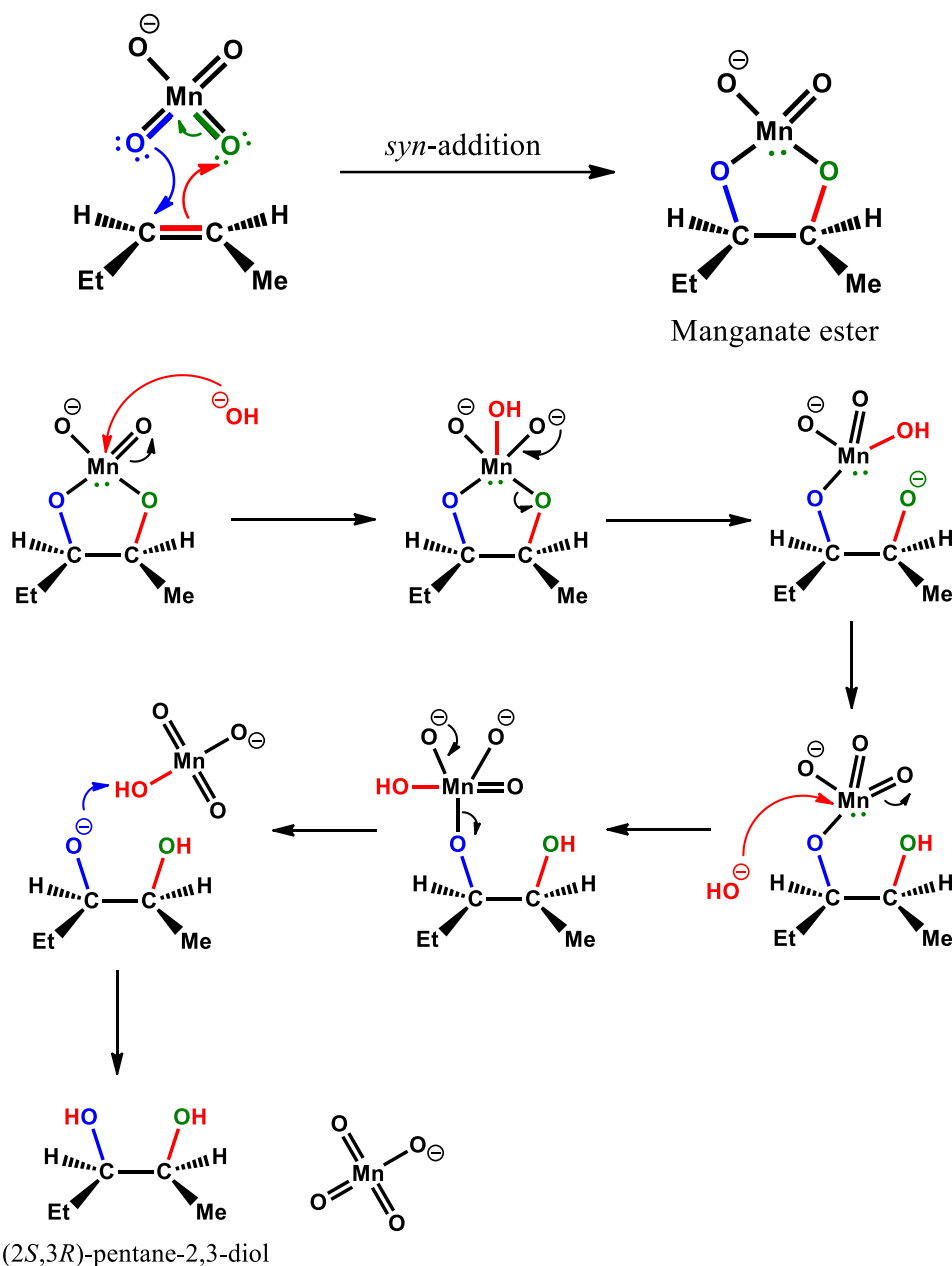
MnO_4^- *dilute*
Cold ; HO^- ; H_2O

cis-diol

Mechanism of Dihydroxylation

Dihydroxylation of alkenes with dilute solution of sodium permanganate $KMnO_4$ occurs at low temperature in a basic mediumand it proceeds in two steps. Initially, permanganate adds to the π bond via a concerted syn-addition resulting in a cyclic manganate ester, which then collapses upon hydrolysis workupforming, as a result, a *cis*-diol.

syn-addition

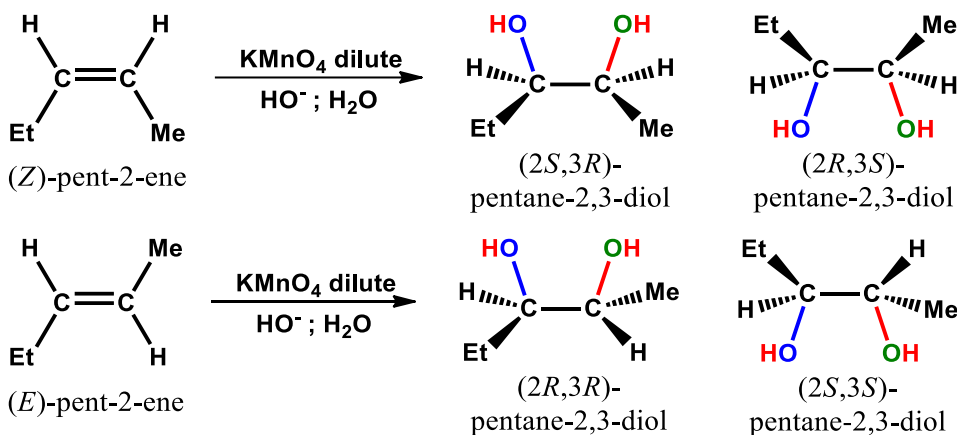
Manganate ester

(2*S*,3*R*)-pentane-2,3-diol

Regiochemistry and Stereochemistry

Just like oxidation with osmium tetroxide, oxidation of alkenes with dilute permanganate and under basic cold condition is a **regiospecific** reaction that proceeds via *syn*-addition and gives *cis*-diols. Furthermore, because the reaction involves a cyclic intermediate where carbon -oxygen bonds form simultaneously,

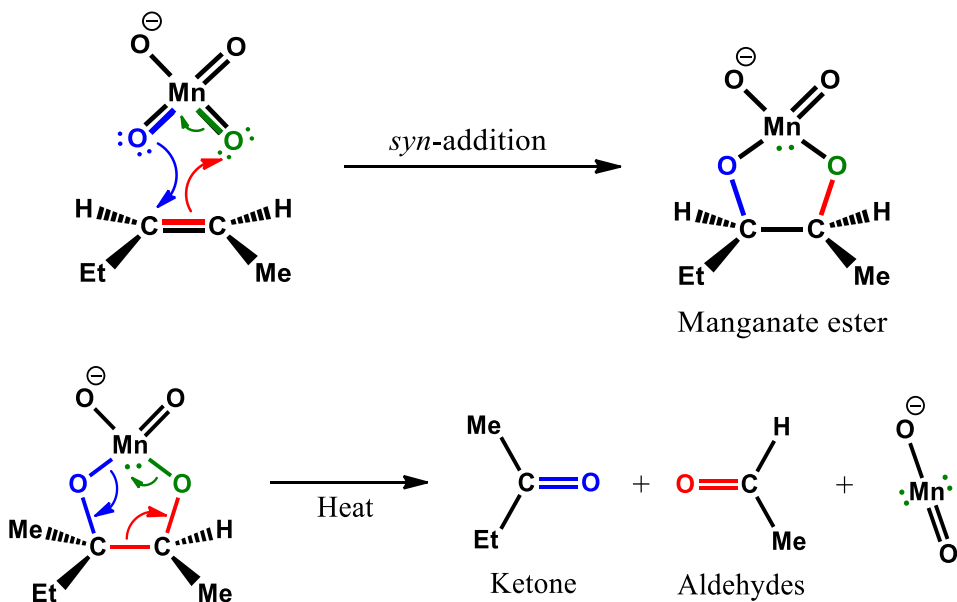
free rotation around σ bond between the oxidized carbon atoms is not possible. As a result, dihydroxylation of asymmetrical alkenes with permanganate is a **stereospecific** reaction. However, since hydroxy groups can add to the π bond from either sides, the reaction is **non-stereoselective**.

(*Z*)-pent-2-ene → ($KMnO_4$ dilute; HO^- ; H_2O) → (2*S*,3*R*)-pentane-2,3-diol + (2*R*,3*S*)-pentane-2,3-diol

(*E*)-pent-2-ene → ($KMnO_4$ dilute; HO^- ; H_2O) → (2*R*,3*R*)-pentane-2,3-diol + (2*S*,3*S*)-pentane-2,3-diol

Mechanism of Oxidative Cleavage

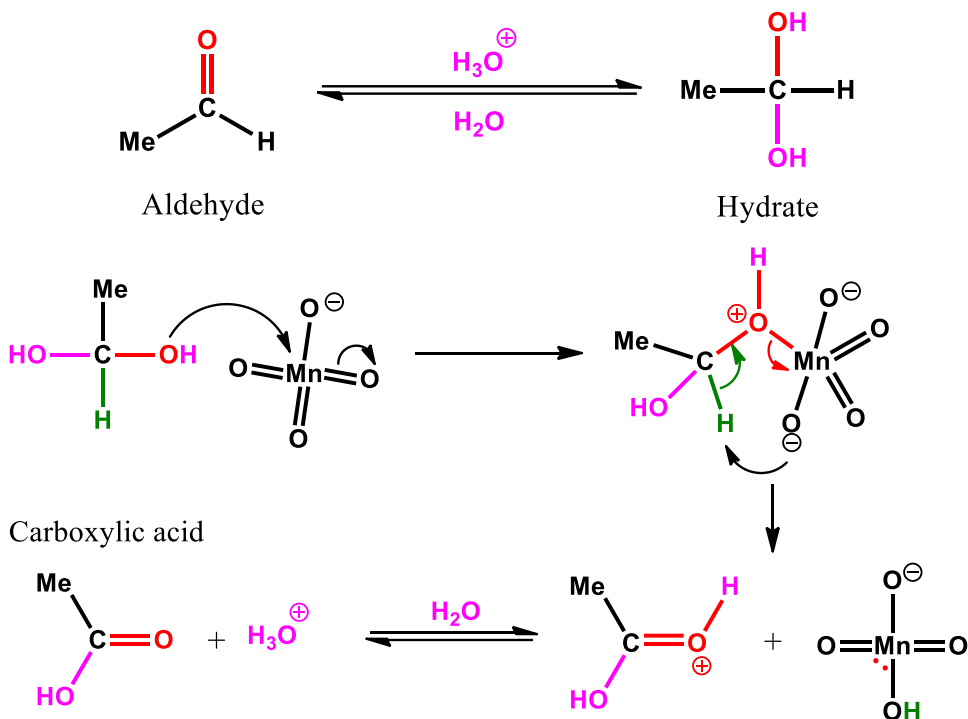
Oxidative cleavage by potassium permanganate occurs in warm acidic conditions with concentrated $KMnO_4$. At first, the reaction gives manganate ester, which then collapses into two carbonyl compounds that can be ketones or aldehydes depending upon the structure of the alkene used.

syn-addition → Manganate ester

Heat → Ketone + Aldehydes

If an aldehyde is produced, further oxidation would take place whereby the aldehyde oxidizes to the corresponding carboxylic acid. In this case, the aldehyde is initially converted to a hydrate intermediate upon acidic hydrolysis workup, which then reacts with permanganate and forms the corresponding carboxylic acid.

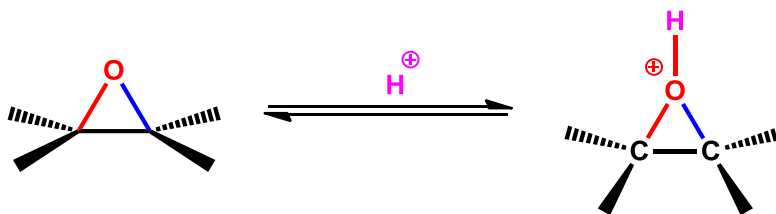
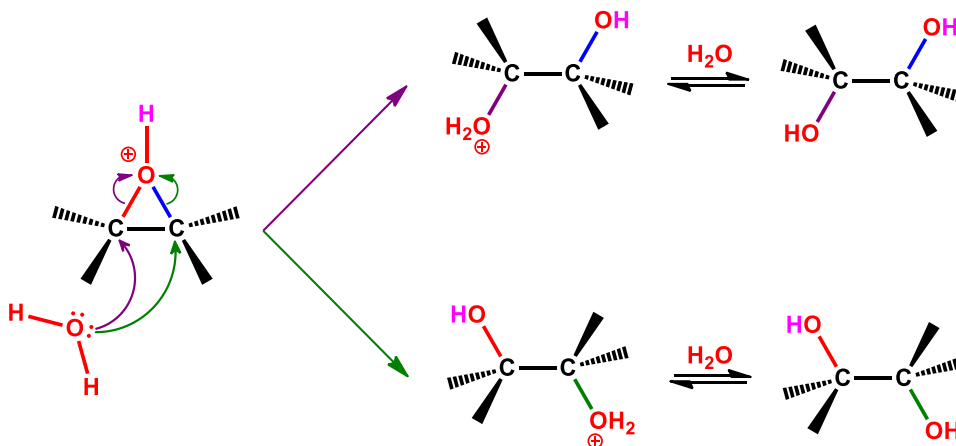
Aldehyde

Hydrate

Carboxylic acid

III. 5. 1. 4. Acid Catalyzed Oxidation of Peroxides

When an alkene reacts with a peroxy acid, a peroxide is formed. This particular reaction is partial oxidation whereby both sp^2 carbons form new covenant bond with the same oxygen. Under aqueous acidic condition, further oxidation occurs as the epoxide ring opens and two hydroxy groups form on vicinal carbon atoms.

Mechanism

Acid catalyzed oxidation of peroxides initially starts by protonation of the peroxide oxygen, which makes carbon-oxygen more polarizable.

The next step is a typical S_N2 reaction where the nucleophile "water" attacks the targeted carbon atom from the opposite side of the leaving group "OH". This process will lead, as a result, to opening the ring and forming an oxonium intermediate, which then gets deprotonated to produce the final glycol.

Regiochemistry and Stereochemistry

Dihydroxylation of an asymmetrical alkene involving a peroxide intermediate is a **regiospecific** reaction whereby hydroxy groups add to vicinal sp_2 exclusively via *anti*-addition giving *trans*-glycols. Furthermore, this particular reaction is **non-stereoselective** because the nucleophile can add to either carbon atoms resulting in a racemic mixture. Nevertheless, since this reaction involves a cyclic intermediate "epoxide", the stereochemistry of the starting material does determine the stereochemistry of the final diol, which makes the reaction **stereospecific**.

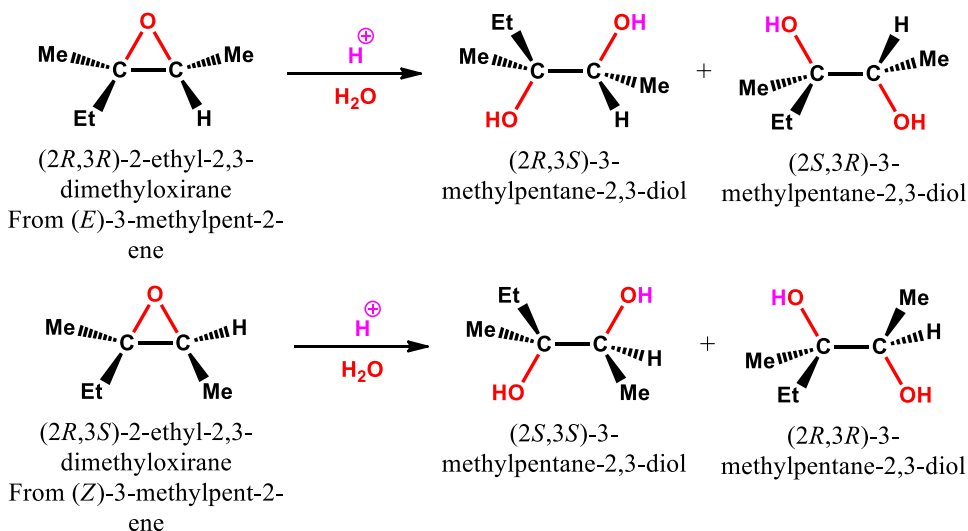
(2*R*,3*R*)-2-ethyl-2,3-dimethyloxirane
From (*E*)-3-methylpent-2-ene

(2*R*,3*S*)-3-methylpentane-2,3-diol

(2*S*,3*R*)-3-methylpentane-2,3-diol

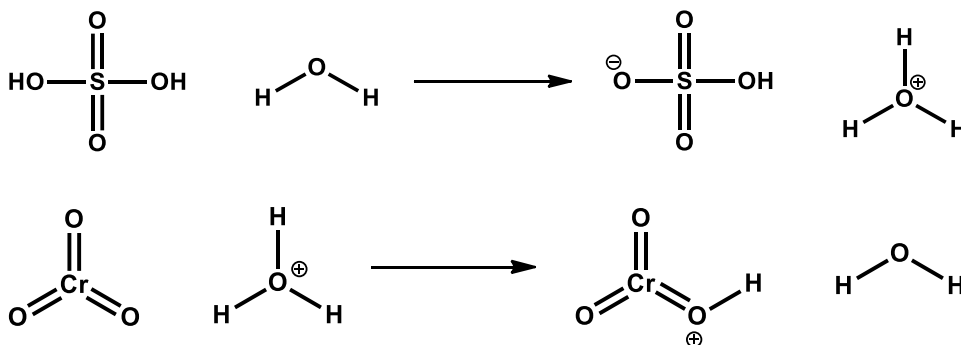
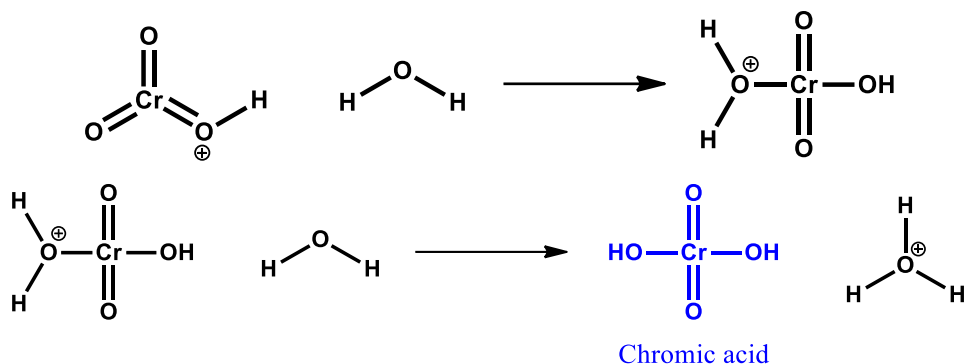
(2*R*,3*S*)-2-ethyl-2,3-dimethyloxirane
From (*Z*)-3-methylpent-2-ene

(2*S*,3*S*)-3-methylpentane-2,3-diol

(2*R*,3*R*)-3-methylpentane-2,3-diol

III. 5. 2. Alcohols

Primary alcohols can yield different products depending upon the oxidizing agent used. Direct oxidation of primary alcohols gives the corresponding aldehydes. In contrast, indirect oxidation initially gives an aldehyde as an intermediate, which then undergoes further oxidation and form the corresponding carboxylic acid. Oxidation of secondary alcohols affords their corresponding ketones regardless of the oxidizing agent.

III. 5. 2. 1. Jones Oxidation

Jones oxidation is a named reaction named after the chemist *Ewart Jones* whereby primary and secondary alcohols oxidize to the corresponding carboxylic acids and ketones, respectively. This reaction was one of the earliest methods to oxidize alcohols and it is carried out with chromic acid, also referred to as Jones reagent, in acetone. Jones reagent is prepared by dissolving chromium trioxide in an aqueous solution of sulfuric acid.

Chromic acid

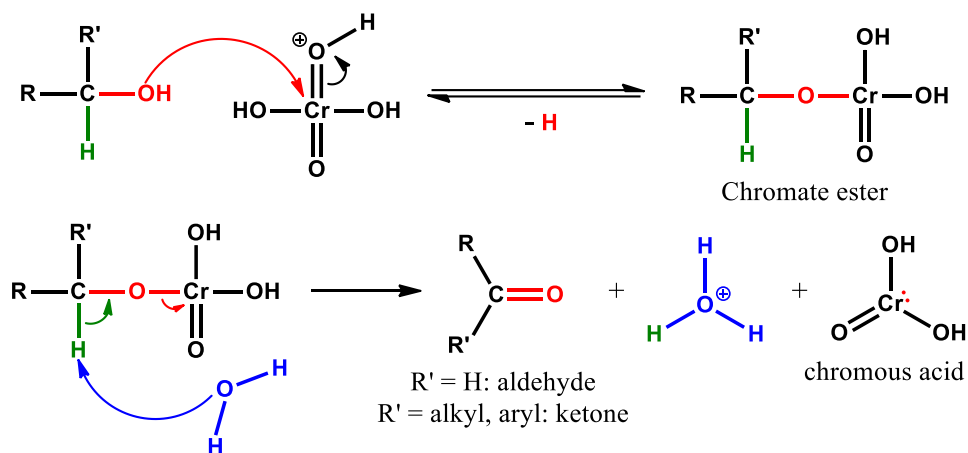
Mechanism

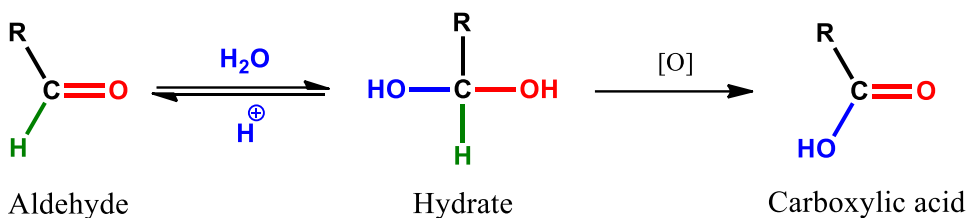
Jones oxidation is initiated by forming chromate ester upon reaction between the alcohol and chromic acid, followed by elimination of a hydrogen proton attached to the carbinol carbon, which leads to the formation of a carbonyl compound.

- H

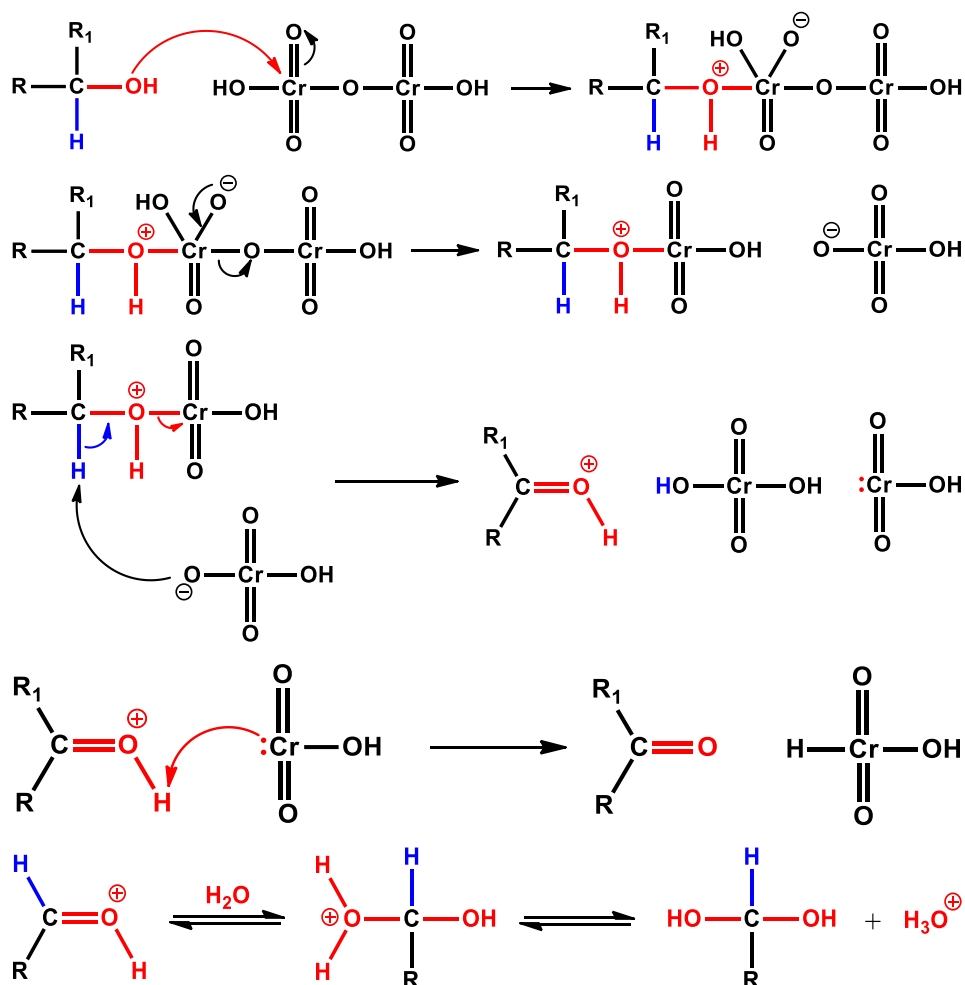
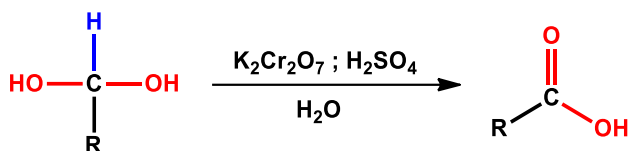
Chromate ester

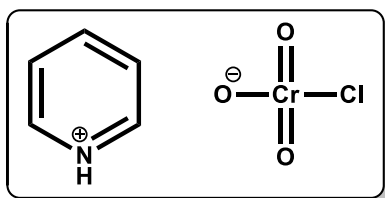
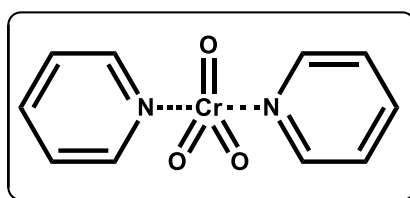
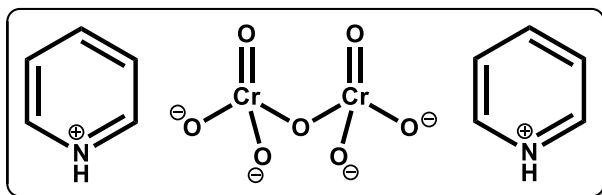
R' = H: aldehyde
R' = alkyl, aryl: ketone

chromous acid

In case of secondary alcohols “R’ = alkyl, or aryl”, the reaction stops at this point where ketone forms. A primary alcohol, on the other hand, initially forms the corresponding aldehyde, which then reacts with water under the acidic condition to form hydrate intermediate. At this point, a further oxidation takes place whereby the hydrate intermediate oxidizes to the corresponding carboxylic acid.

Aldehyde Hydrate Carboxylic acid

III. 5. 2. 2. With $K_2Cr_2O_7$ ($Na_2Cr_2O_7$) ; H_2SO_4

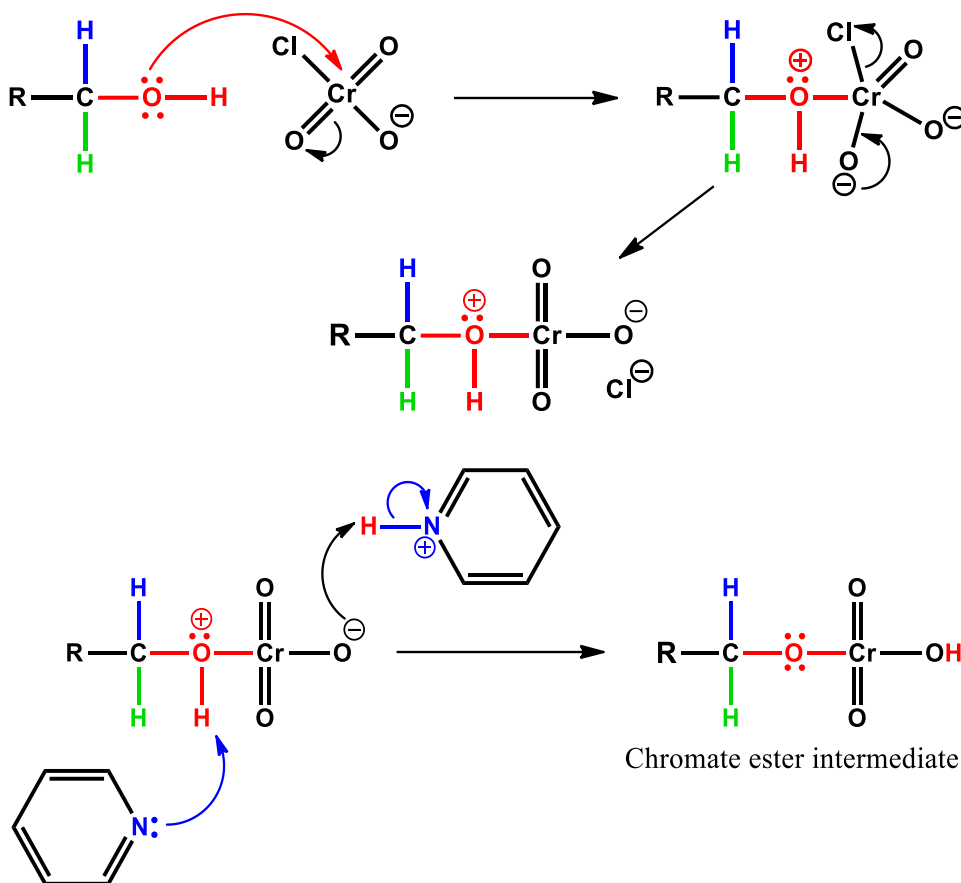
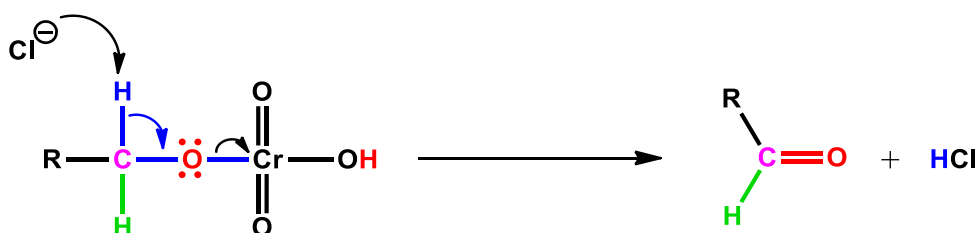
Oxidation of primary and secondary alcohols with $K_2Cr_2O_7$ or $Na_2Cr_2O_7$ under acidic conditions follows the same mechanism of Jones oxidation and gives the same products.

$$HO-C(H)(R)-OH \xrightarrow[H_2O]{K_2Cr_2O_7\ ;\ H_2SO_4} R-C(=O)-OH$$

III. 5. 2. 3. Oxidation with Chromium-Based Reagents

Direct oxidation of primary alcohols is carried out with chromium -based reagents such as PCC, PDC, and Sarett / Collins reagent. If a secondary alcohol is involved, a ketone forms instead.

Pyridinium chlorochromate (PCC)

Sarett / Collins reagent

Pyridinium dichromate (PDC) : Cornforth reagent

Mechanism with PCC

Pyridinium chlorochromate (PCC) is a strong oxidizing agent that converts primary and secondary alcohols into their corresponding carbonyl compounds; aldehydes and ketones , respectively . Oxidation with PCC must be carried out with non - aqueous solvent such as CH_2Cl_2 in order to prevent further oxidation of the aldehyde formed. The first step of this reaction involves nucleophilic attack of the alcohol hydroxy gro up on the chlorochromate followed by hydrogen rearrangement, which leads to the formation of a chromate ester intermediate.

Chromate ester intermediate

The final step consists in eliminating the acidic hydrogen atom from the chromate ester intermediate, which results in the formation of an aldehyde.

III. 5. 2. 4. Oxidation with Sodium Hypochlorite NaOCl

Even though primary and secondary alcohols can be oxidized by several oxidizing agents, it is always better to choose an environmentally benign and economical

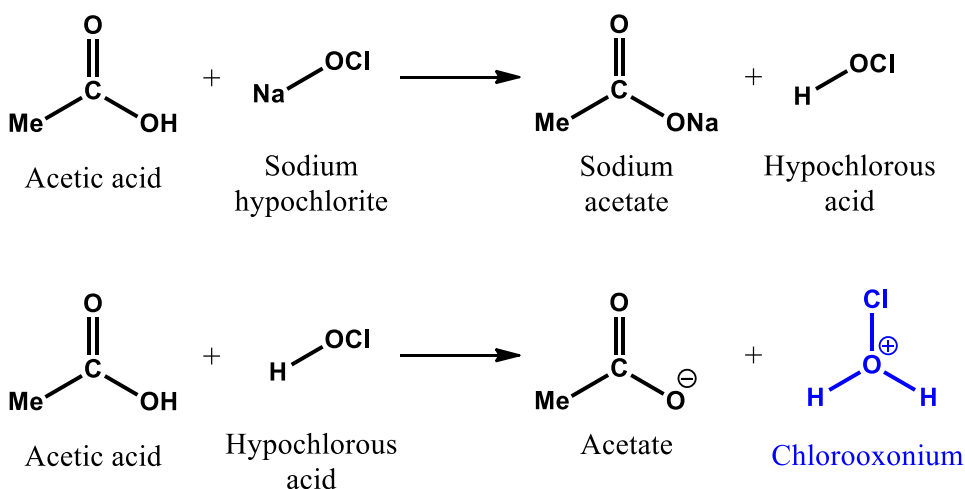
oxidant. Oxidation with sodium hypochlorite meets these requirements. It is less toxic in comparison to chromium-based reagents, economical, and efficient oxidizing agent that gives high yields. Furthermore, depending upon reaction conditions, sodium hypochlorite can oxidize primary alcohols to the corresponding aldehydes, or selectively oxidizes secondary alcohols to their corresponding ketones in the presence of primary alcohols.

Mechanism with Acetic Acid

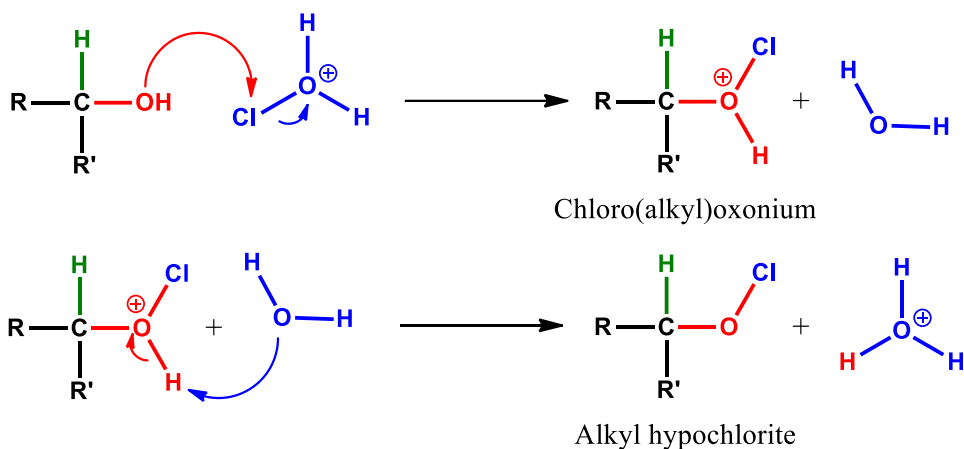
Sodium hypochlorite in aqueous solution of acetic acid oxidizes secondary alcohols to their corresponding ketones. Primary alcohols, on the other hand, are initially oxidized to aldehydes, which then react with other primary alcohol molecules and form dimeric esters. However, this reaction occurs much more slowly than in case of secondary alcohols.

Oxidation of secondary alcohols with sodium hypochlorite in the presence of acetic acid proceeds in three steps. The first step consists in generating the reactive chlorooxonium intermediate. At this point, sodium hypochlorite reacts with acetic acid resulting in a hypochlorous acid, which then gets protonated creating the reactive intermediate.

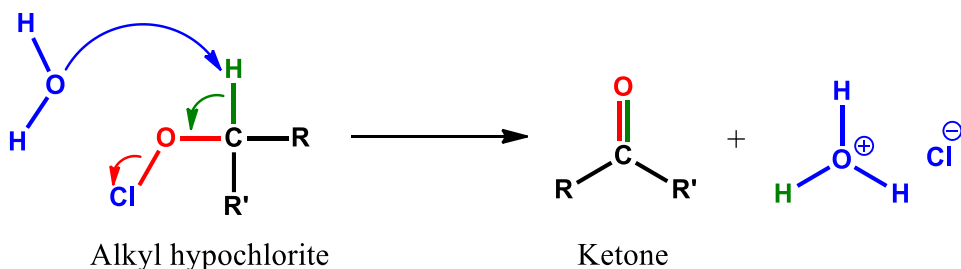
MeC(=O)OH (Acetic acid) + NaOCl (Sodium hypochlorite) → MeC(=O)ONa (Sodium acetate) + HOCl (Hypochlorous acid)

MeC(=O)OH (Acetic acid) + HOCl (Hypochlorous acid) → $MeC(=O)O^{-}$ (Acetate) + $H_2O^{+}Cl$ (Chlorooxonium)

In the next step, the secondary alcohol reacts with chlorooxonium to form alkyl hypochlorite intermediate.

Chloro(alkyl)oxonium

Alkyl hypochlorite

The final step consists in eliminating HCl from the alkyl hypochlorite, which leads to the formation of the corresponding ketone. At this point, a base such as acetate or water would abstract a hydrogen proton from the carbinol carbon resulting in the formation of carbon-oxygen double bond.

Alkyl hypochlorite

Ketone

Primary alcohols follow the same mechanism of secondary alcohols oxidation. Nevertheless, the aldehydes formed would react with other primary alcohol molecules and form hemiacetals. At this point, further oxidation would take place whereby the hydroxy group oxidizes to a carbonyl giving, as a result, a dimeric ester.

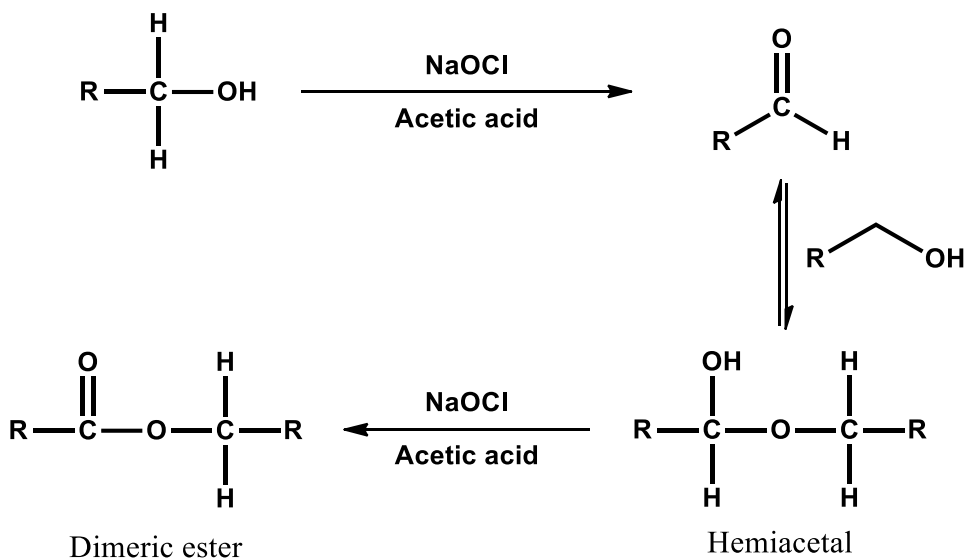
NaOCl

Acetic acid

NaOCl

Acetic acid

Dimeric ester

Hemiacetal

Mechanism with TEMPO

Primary alcohols can be oxidized to their corresponding aldehydes when the reaction is catalyzed by TEMPO “(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl”. This reaction proceeds through a catalytic cycle with stoichiometric amount of sodium hypochlorite, which oxidizes TEMPO into the *N*-oxoammonium salt, which then oxidizes the primary alcohol to the corresponding aldehyde.

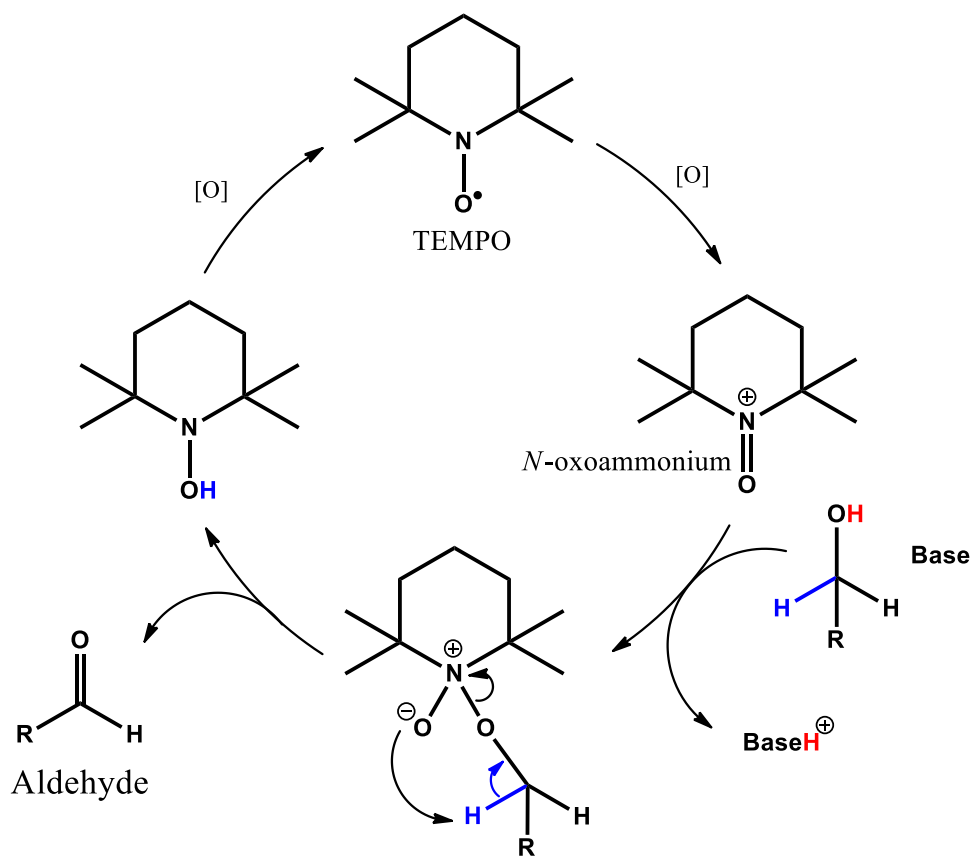
[O]

TEMPO

[O]

N-oxoammonium

Base

BaseH

Aldehyde

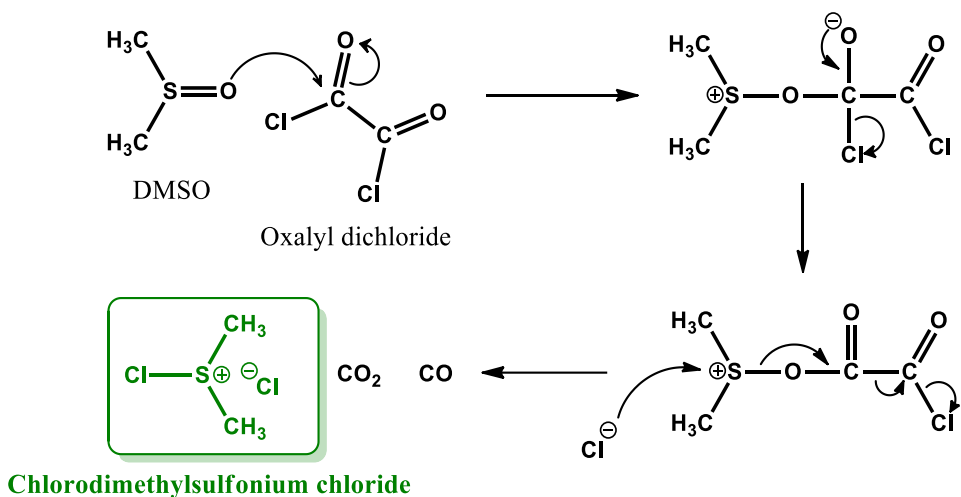
III. 5. 2. 5. Swern Oxidation

Swern oxidation is a chemoselective reaction named after the American chemist *Daniel Swern* whereby primary alcohols oxidize to the corresponding aldehydes while secondary alcohols oxidize to ketones. This reactioris carried out withoxalyl dichloride and dimethylsulfoxide DMSO, which react with each other and produce the reactive reagent "chlorodimethylsulfonium chloride".

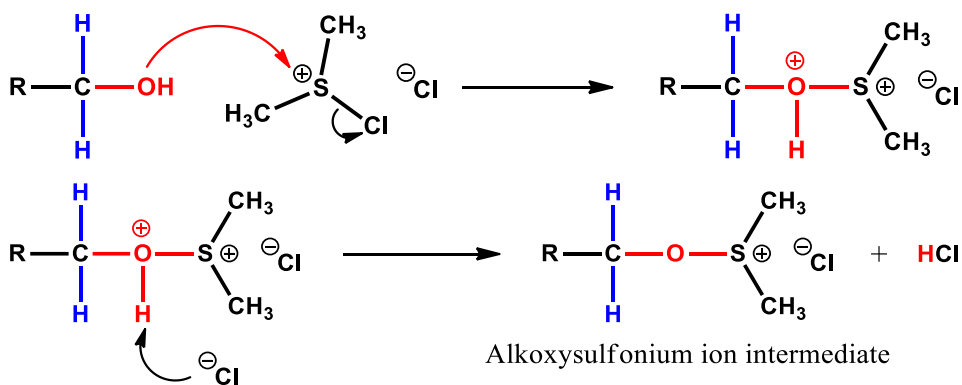
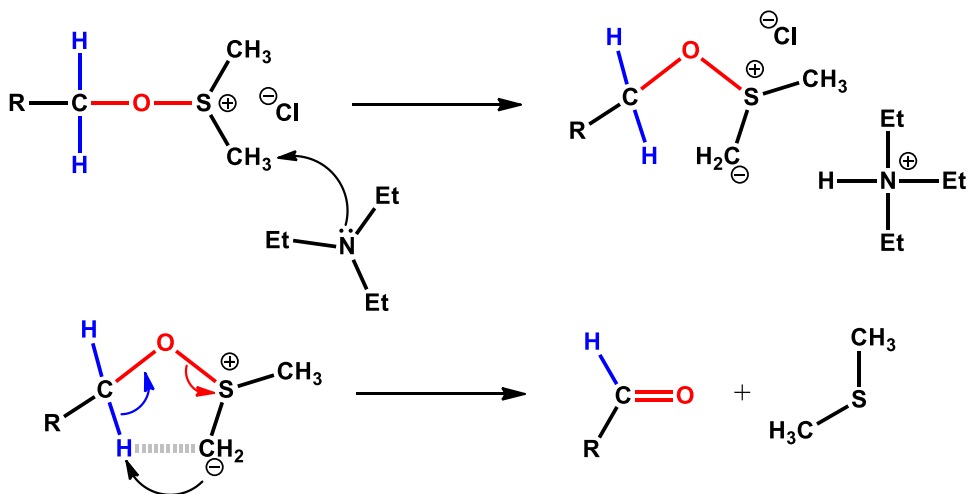
DMSO

Oxalyl dichloride

CO_2 CO

Chlorodimethylsulfonium chloride

Mechanism

Swern oxidation reaction is initiated by nucleophilic attack of alcohol hydroxy group on the positively charged sulfur atom of chl orodimethylsulfonium chloride resulting in an ionic intermediate. Later on, chloride ion would abstract hydrogen proton from the ionic intermediate leading to the formation of an alkoxysulfonium ion intermediate.

Alkoxysulfonium ion intermediate

The next step consists i n deprotonating a methy group attached to sulfur with an organic base, usually triethylamine Et_3N, which leads to the formation of a carbanion intermediate forms. At this point, the negatively charged carbon atom abstracts a hydrogen proton from the carbin ol carbon, which gives rise to the corresponding aldehyde.

Summary

Alcohol	Reagent	Product
Primary alcohol	PCC PDC in DMF Collins Oxidation Sarett Oxidation Swern oxidation NaOCl; TEMPO	Aldehyde
	Jones reagent $K_2Cr_2O_7$; H_2SO_4 $KMnO_4$; HO^- ; H_2O	Carboxylic Acid
Secondary alcohol	Any potent oxidizing agent	Ketone

III. 6. Reduction Reactions

III. 6. 1. Reduction of Alkenes and Alkynes

Reduction of alkenes and alkynes can be accomplished by catalytic hydrogenation, or with alkali metals in liquid ammonia.. *(See concerned addition; hydrogenation page 178).*

III. 6. 2. Reduction of Benzene

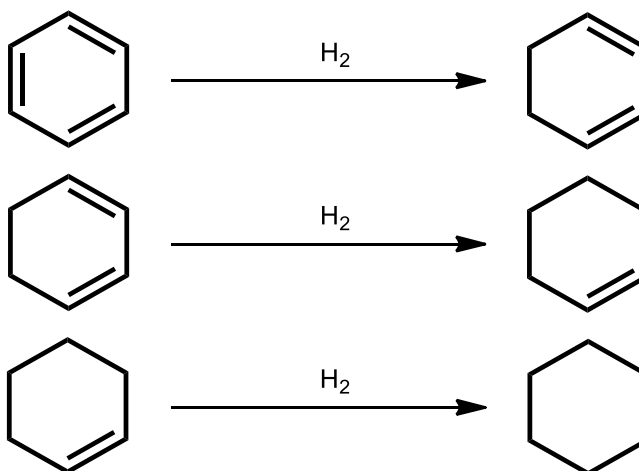
The most common methods to reduce benzene and its derivatives is catalytic hydrogenation, which gives fully saturated compound, or via Birch reaction, which yields partially unsaturated rings.

III. 6. 2. 1. Catalytic Hydrogenation

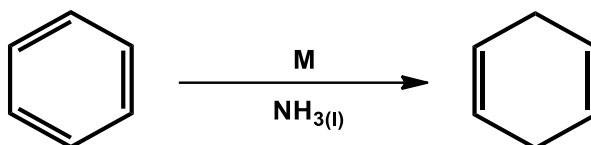
Due to its aromaticity, benzene ring is so stable and thus, it undergoes catalytic hydrogenation only under extreme conditions such as high pressure and temperature.

Depending upon the catalyst used, tem perature and pressure can vary in each reaction. Catalytic hydrogenation with Rh or Pt is usually carried at 5 to 10 atm of hydrogen pressure and at 50 to 100 °C. On the other hand, Ni and Pd are efficient under 100 to 200 atm and between 100 to 200 °C.

➲ ***Example***

Reduction of benzene and its derivatives to cyclohexane compounds proceeds in three steps. At first, the benzene ring acquires two hydrogen atoms resulting in a 1,3-cyclohexadiene, which then reacts with two hydrogen atoms giving cyclohexene. Finally, cyclohexene r

III. 6. 2. 2. Birch Reduction

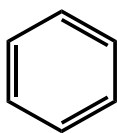
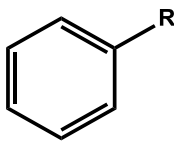
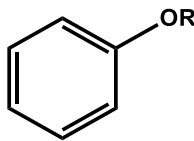
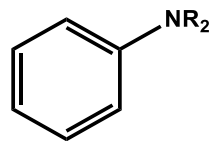
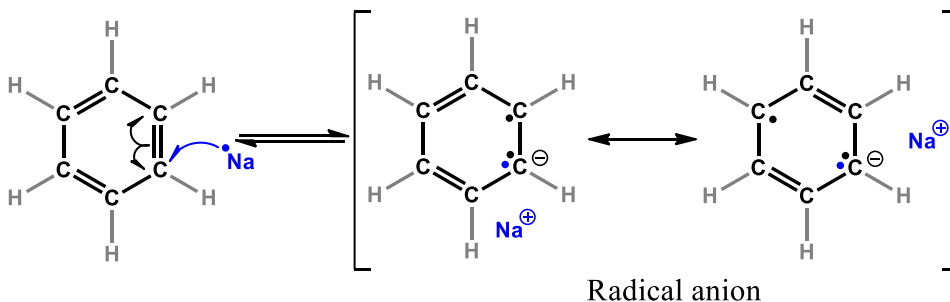
Birch reduction is one of the most useful reactions in organic synthesis. It consists in converting benzene ring into a c yclohexadiene. This reaction was named after the Australian chemist *Arthur Birch* and it is carried out with an alkali metal, usually lithium or sodium, in liquid ammonia. Dissolved alkali metal in liquid ammonia creates an excellent reducing medium for aromatic rings since it provides solvated electrons. Moreover, Birch reaction may also involve other co -solvents such as ether and THF, which improve the solubility of reactants and serve as hydrogen proton sources.

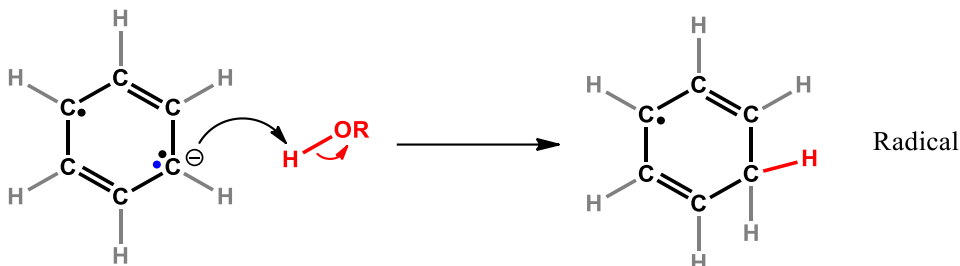
$$\text{Benzene} \xrightarrow[NH_{3(l)}]{M} \text{Cyclohexadiene}$$

Mechanism

Aromatic compounds are divided into three classes according to their Birch reduction behavior.

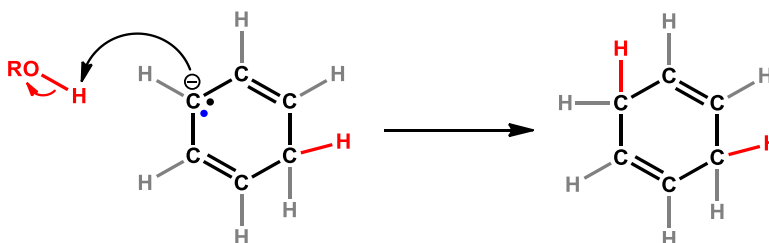
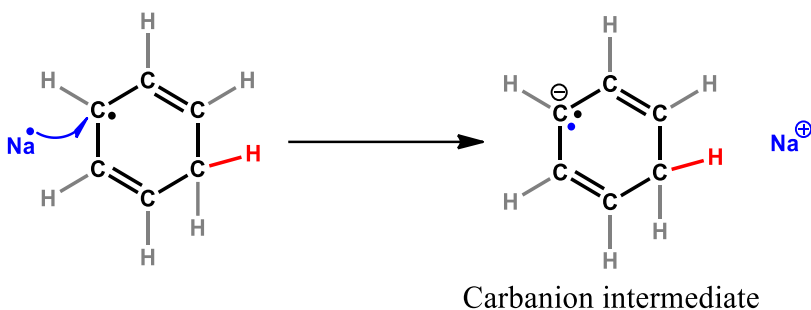
Class 1

The first class includes benzene and its inactivated derivatives such as alkylbenzenes, aryl ethers, and aminobenzenes.

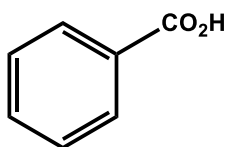
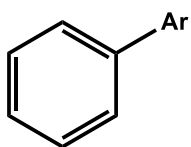
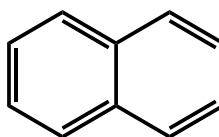
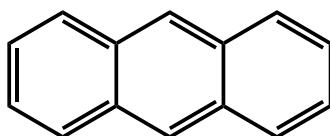
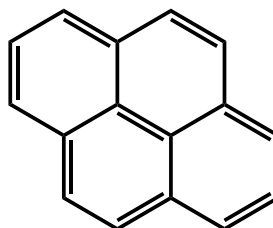
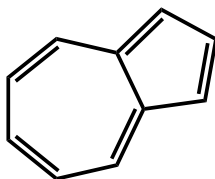
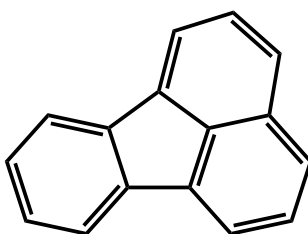
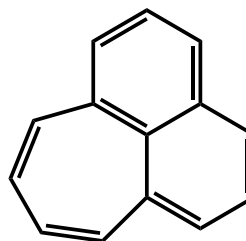
R, OR, NR_2

Benzene | Alkylbenzene | Aryl ethers | Aminobenzenes

For these compounds, the reaction requires alcohol as proton supply. Initially, the aromatic ring accept one electron from the alkali metal present in the solution, which creates a radical anion intermediate.

Radical anion

In the next step, the radical anion intermediate would abstract a hydrogen proton usually from the alcohol forming a radical species.

Radical

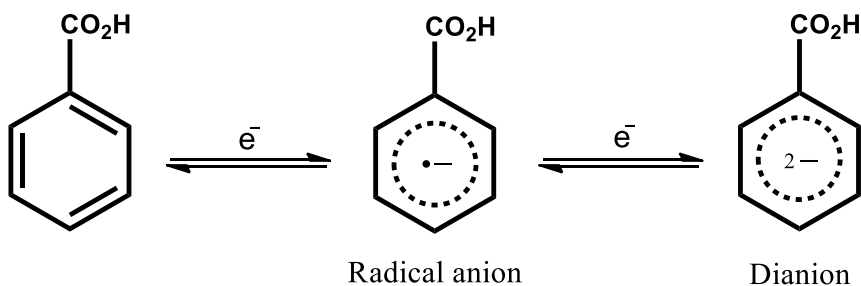
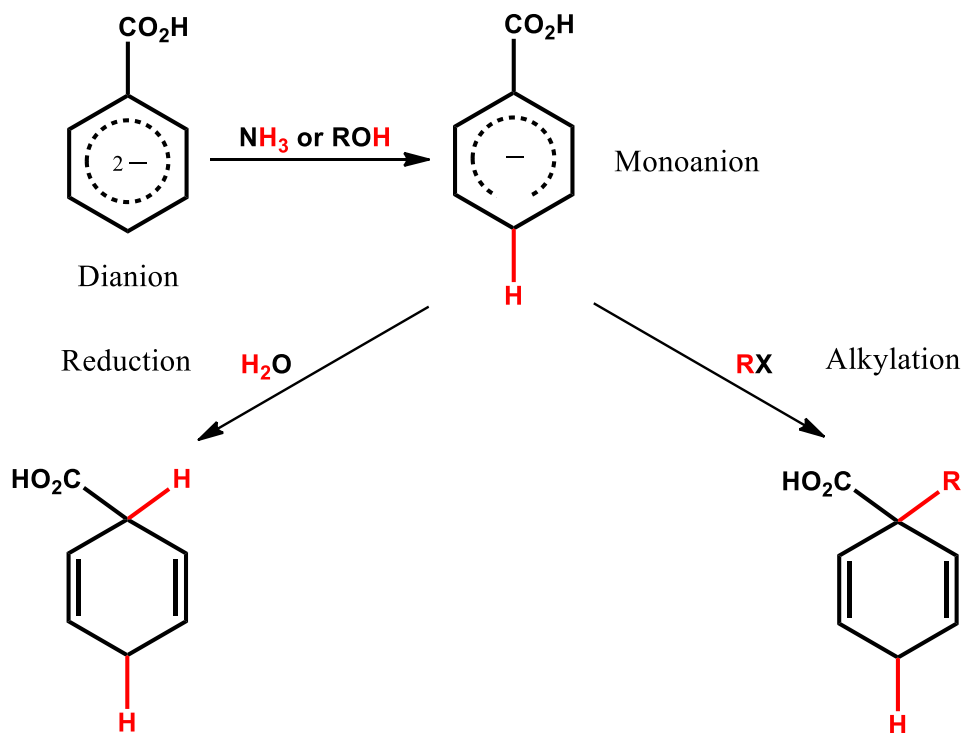
Later on, the radical intermediate would receive an electron from the alkali metal resulting in a carbanion intermediate, which then abstracts a hydrogen proton from a nearby alcohol to yield a cyclohexadiene. In this case, alkylation of the anionic intermediate is not possible.

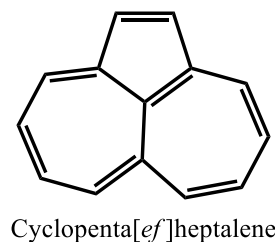
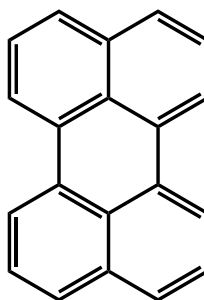
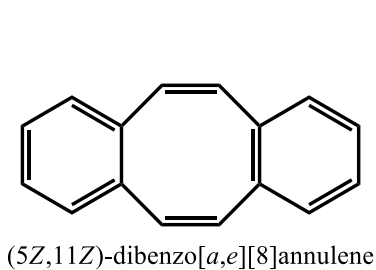
Carbanion intermediate

Class 2

The second class comprises activated benzene derivatives such as benzoates and biphenyls, and several polynuclear aromatic systems with two to four fused rings. In contrast to compounds of the first type, the use of alcohol is not necessary and in some cases, it should be avoided in order to prevent over-reduction.

CO_2H Ar

Benzene Alkylbenzene Naphthalene

Anthracene Pyrene

Azulene Fluoranthene Cyclohepta[*de*]naphthalene

Birch reduction of class 2 compounds starts by forming a radical anion, which then accepts a second electron from the alkali metal resulting in a dianion intermediate.

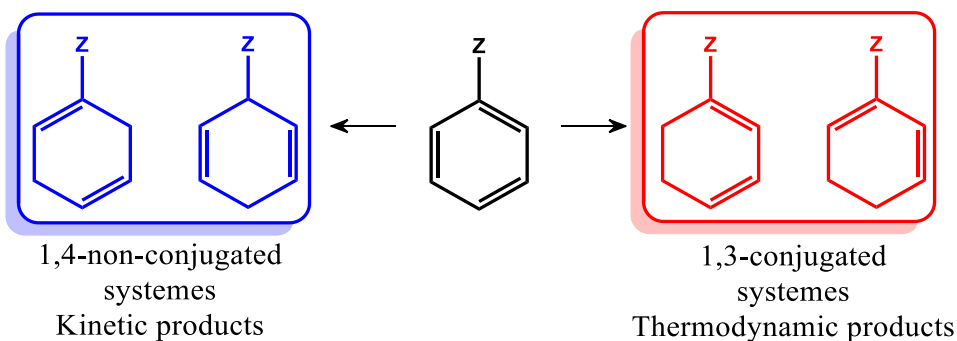
CO_2H e^- CO_2H e^- CO_2H

Radical anion Dianion

The following step consists in protonating the dianion intermediate usually by liquid ammonia resulting in a monoanion intermediate, which then gets protonated by water. In addition to protonation, alkylation of the final monoanion intermediate can also take place when given the right reagent.

Class 3

Large polynuclear compounds such as perylene, and compounds that exhibit aromaticity when they form dianion intermediate such as cyclooctatetraene belong to class 3 systems. These compounds tend to be resistant to protonation by liquid ammonia. Nevertheless, alkylation, dialkylation, and even trialkylation can readily occur with these compounds.

Regiochemistry

In general, Birch reduction of benzene derivatives affords non-conjugated systems, which represent the kinetic products. Nevertheless, in some cases, the thermodynamic products are also observed.

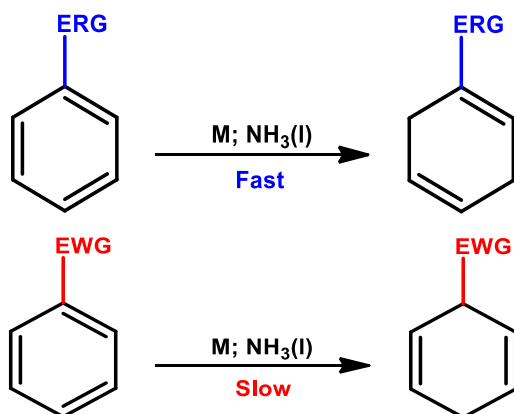
1,4-non-conjugated systemes
Kinetic products

1,3-conjugated systemes
Thermodynamic products

Moreover, the nature of substituents does affect the reaction rate where electron-withdrawing groups enhance the reaction rate while electron-releasing groups decrease it. In terms of regiochemistry, Birch proposed a rule to determine on which carbon atom the reaction is more likely to take place.

Birch's Rule

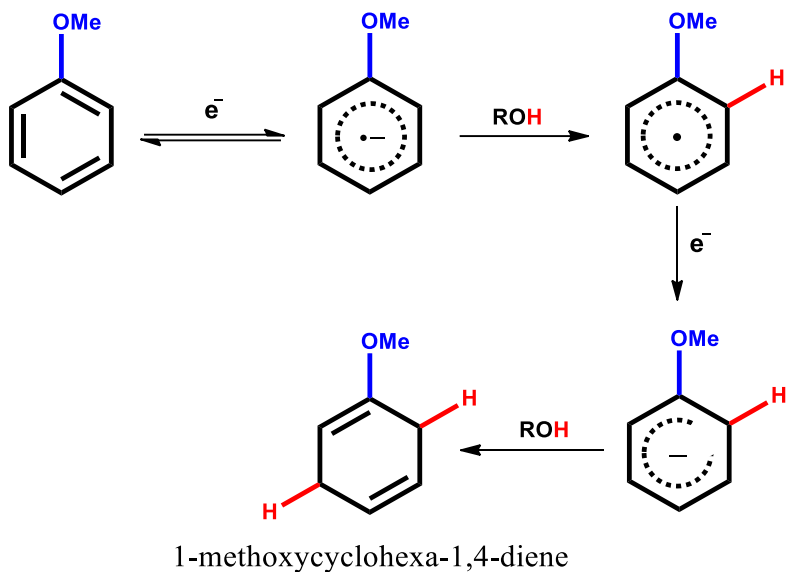
Birch's rule states that ERG substituents direct reduction so the predominant product would have the maximum number of these substituents attached to vinylic carbon atoms. On the other hand, EWG substituents direct reduction so the predominant product would have the maximum number of these substituents attached to allylic carbon atoms.

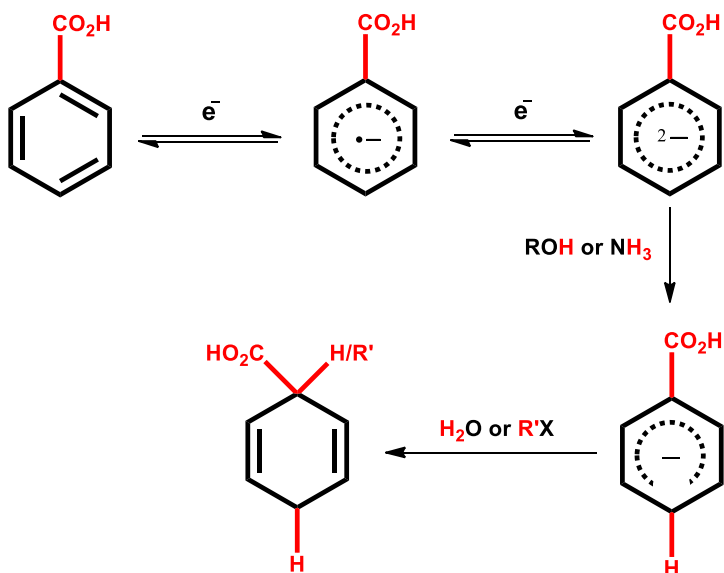
ERG → M; NH_3(l), Fast → ERG

EWG → M; NH_3(l), Slow → EWG

➲ ***Example***

Birch reduction of anisole gives 1-methoxycyclohexa-1,4-diene.

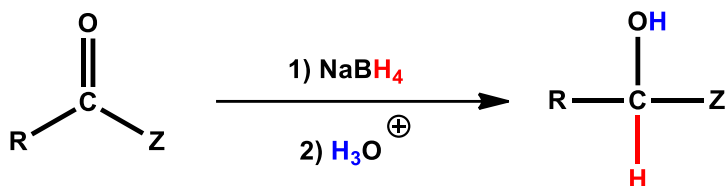
OMe e⁻ ROH H e⁻ OMe H ROH OMe H H

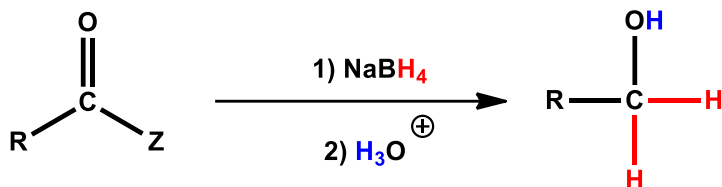
1-methoxycyclohexa-1,4-diene

Birch reduction of benzoic acid yieldscyclohexa-2,5-dienecarboxylic acid while 1-methylcyclohexa-2,5-dienecarboxylic acid.

CO_2H e⁻ CO_2H e⁻ CO_2H 2— ROH or NH_3 CO_2H H H_2O or R'X HO_2C H/R' H

III. 6. 3. Reduction of Carbonyl Compounds

III. 6. 3. 1. With $NaBH_4$ and $LiBH_4$

$NaBH_4$ is a mild reducing agent that reduces aldehydes, ketones, and acyl halides into alcohols. In addition to these compounds, $LiBH_4$ reduces esters into primary alcohols. Reduction with $NaBH_4$ or $LiBH_4$ is usually performed in polar pro tic solvent such as water or methanol, which serves as hydrogen proton donor.

1) $NaBH_4$
2) $H_3O^{\oplus}$

Z = H: aldehyde; pripary alcohol
Z = Alkyl : ketone; secondary alcohol

1) $NaBH_4$
2) $H_3O^{\oplus}$

Z = Halogen: acyl halide; pripary alcohol

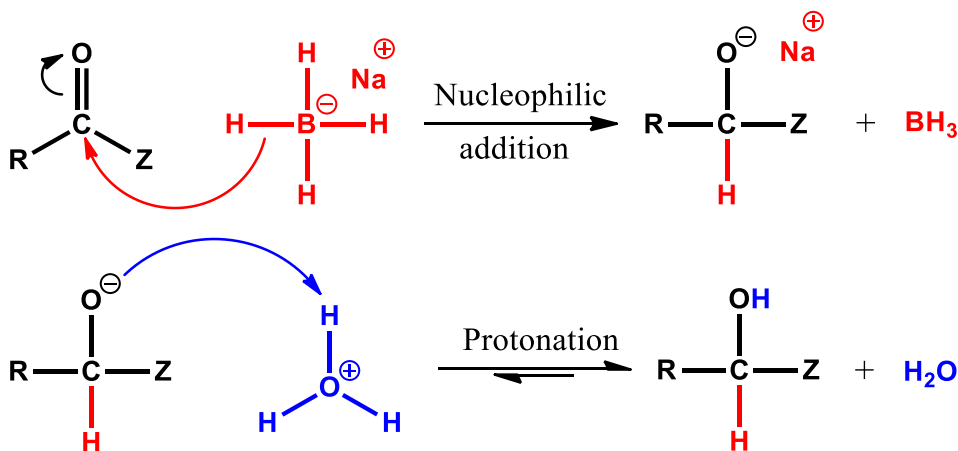
General Mechanism

For aldehydes and ketones, the reaction proceeds via nucleophilic addition where hydride io n adds to the carbonyl carbon resulting in a tetr ahedral intermediate, which then get protonated under acidic or basic condition.

Nucleophilic addition

$+ BH_3$

Protonation

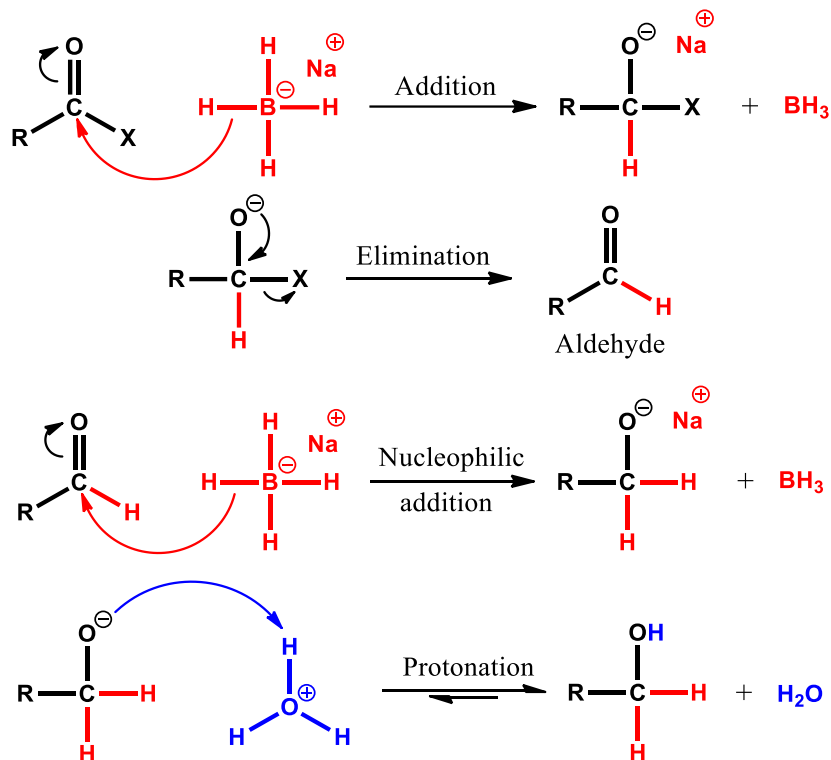
$+ H_2O$

For acyl halides, the reaction proceeds in two steps. Initially, the halogen gets displaced by hydrogen atom through nucleophilic substitution reaction, which yields an aldehyde. In the next step, the aldehyde formed undergoes nucleophilic addition followed by protonation to give the corresponding primary alcohol.

Addition

Elimination

Aldehyde

Nucleophilic addition

Protonation

Furthermore, reduction of a prochiral carbonyl compound with $NaBH_4$ yields a stereoisomeric mixture, which makes the reaction **non-stereoselective**.

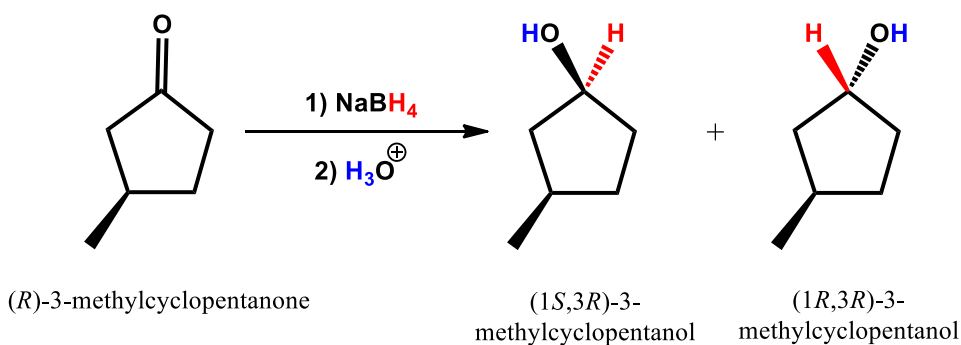
➲ ***Examples***

1) $NaBH_4$

2) $H_3O^{\oplus}$

(*R*)-3-methylcyclopentanone

(1*S*,3*R*)-3-methylcyclopentanol

(1*R*,3*R*)-3-methylcyclopentanol

III. 6. 3. 2. With $LiAlH_4$

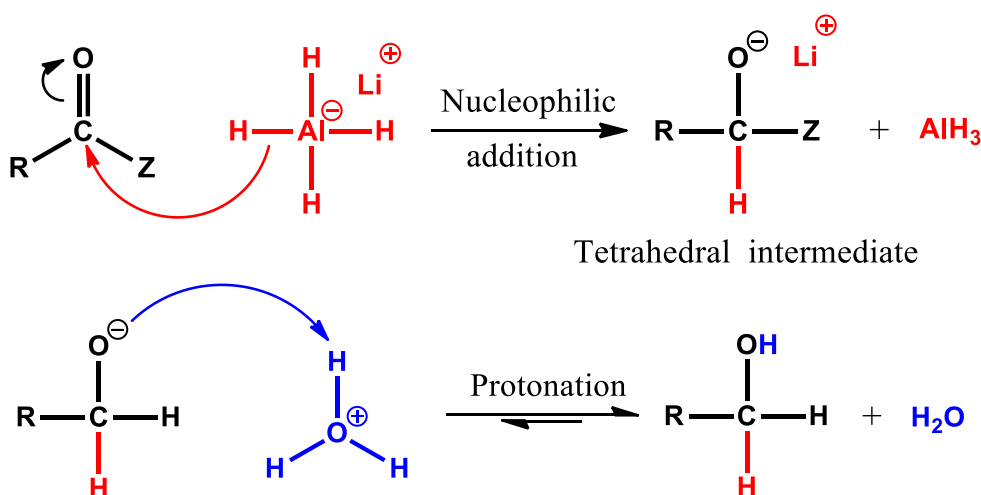
Lithium aluminium hydride (LAH) is a potent reducing agent that can reduce all carbonyl compounds into their corresponding alcohols, nitriles to amines, and even α, β–unsaturated carbonyl compounds. In contrast to sodium borohydride, $LiAlH_4$ should not be used in a hydroxylic solvent such as water otherwise; it will react violently with the solvent.

Aldehydes and ketones

Reduction of aldehydes and ketones with $LiAlH_4$ gives primary and secondary alcohols, respectively. This reaction follow the same mechanism of $NaBH_4$. However, in this case, after the first step is completed, water or dilute acid is carefully added to protonate the alkoxide intermediate.

$$R(Z)C{=}O + Li^{+}\,[AlH_4]^{-} \xrightarrow[\text{addition}]{\text{Nucleophilic}} R{-}C(O^{-})(H){-}Z\;Li^{+} + AlH_3$$

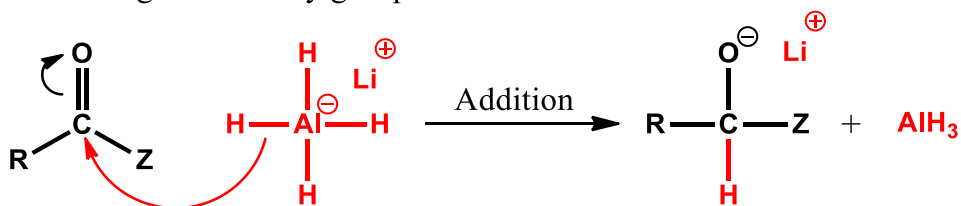
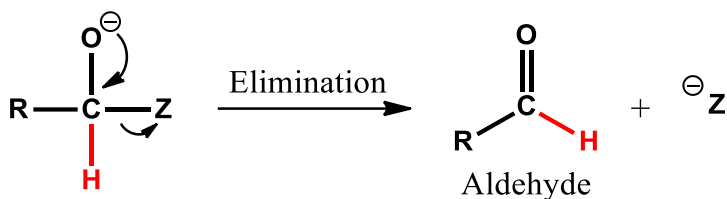
Tetrahedral intermediate

$$R{-}C(O^{-})(H){-}H + H_3O^{+} \underset{}{\overset{\text{Protonation}}{\rightleftharpoons}} R{-}C(OH)(H){-}H + H_2O$$

Esters and Acyl Halides

Reduction of carboxylic esters and acyl halides with $LiAlH_4$ yields primary alcohols. This reaction initially produces an alde hyde intermediate through nucleophilic substitution react ion whereby the leaving group gets displaced by hydride ion.

Z = halogen or alkoxy group

$$R(Z)C{=}O + Li^{+}\,[AlH_4]^{-} \xrightarrow{\text{Addition}} R{-}C(O^{-})(H){-}Z\;Li^{+} + AlH_3$$

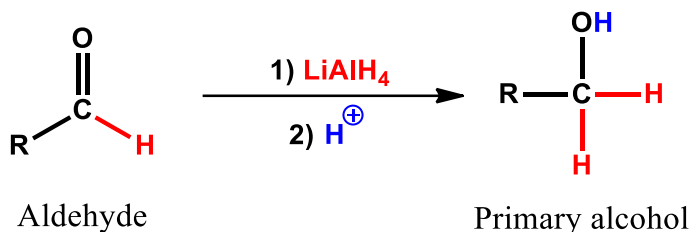
Elimination

Aldehyde

Because $LiAlH_4$ is a strong reducing agent, the aldehyde formed would u ndergo further reduction to the corresponding primary alcohol.

1) $LiAlH_4$

2) $H^{\oplus}$

Aldehyde

Primary alcohol

Carboxylic Acids

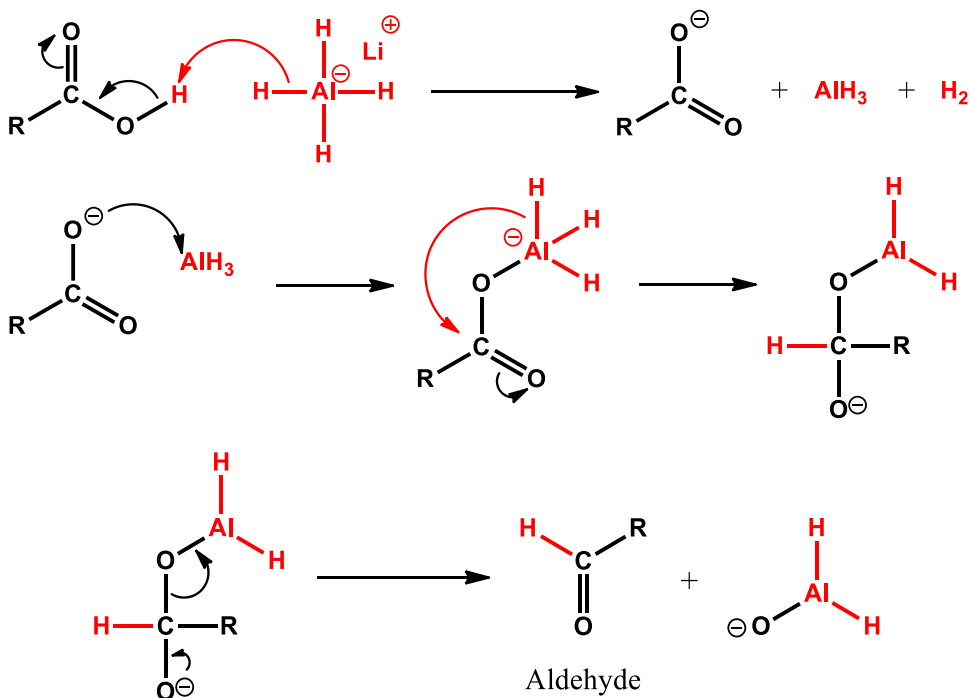
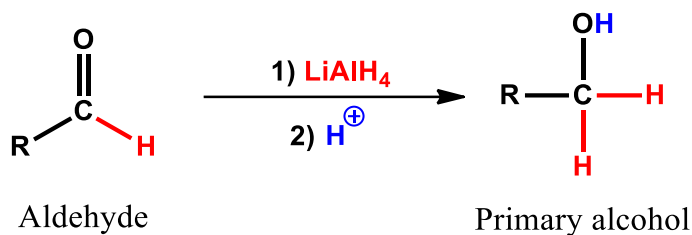
In case of carboxylic acids, the hydride ion would abstract a hydrogen proton from the hydroxy group resulting in a carboxylate intermediate and hydrogen gas. Later on, the carboxylate react s with aluminium trihydride to form an aldehyde, which then reacts with $LiAlH_4$ and form a primary alcohol.

$+ AlH_3 + H_2$

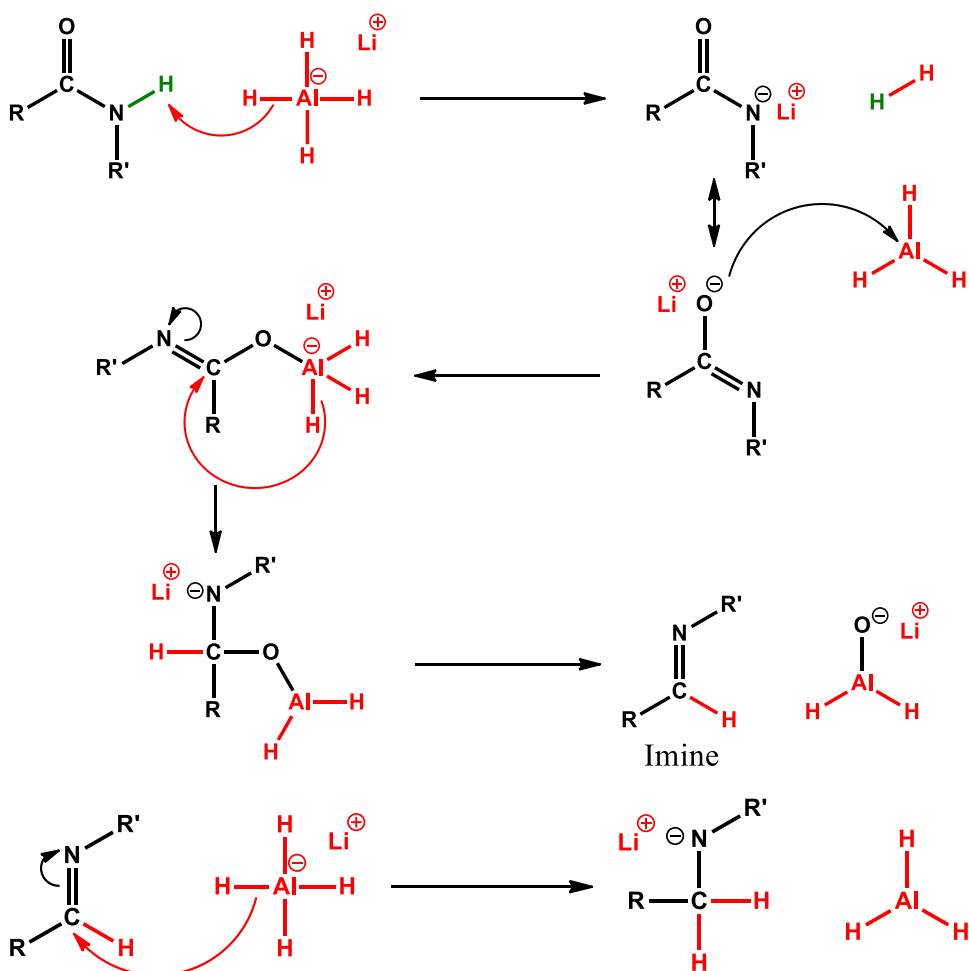
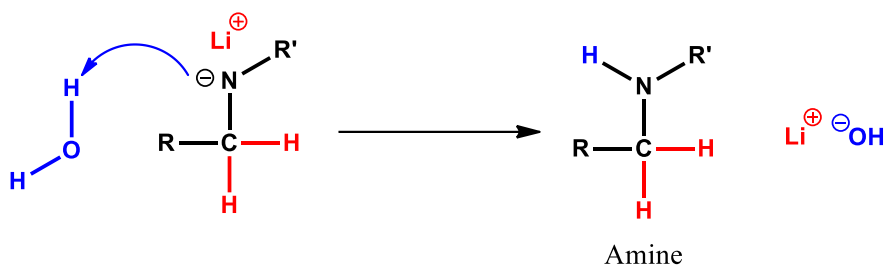
Aldehyde

1) $LiAlH_4$
2) $H^{\oplus}$

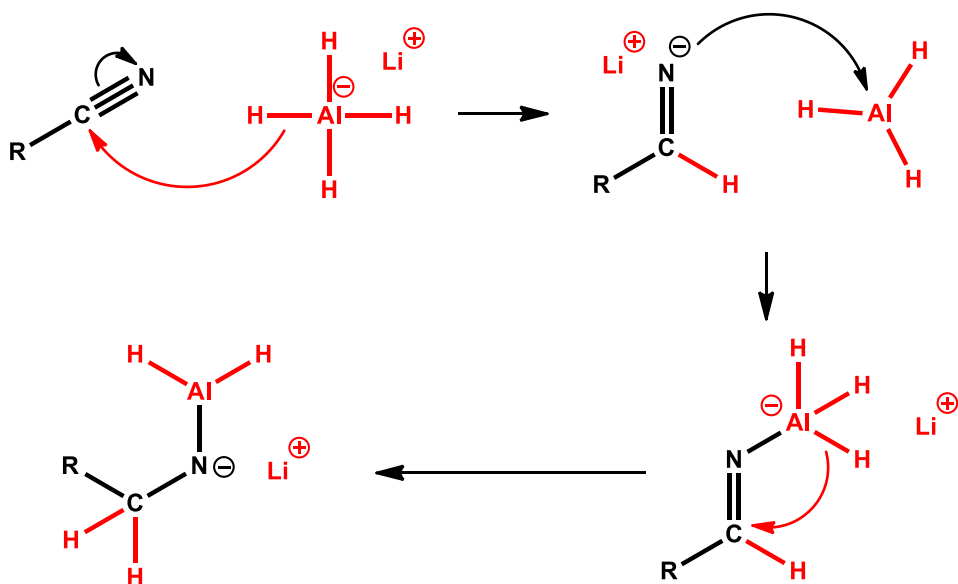
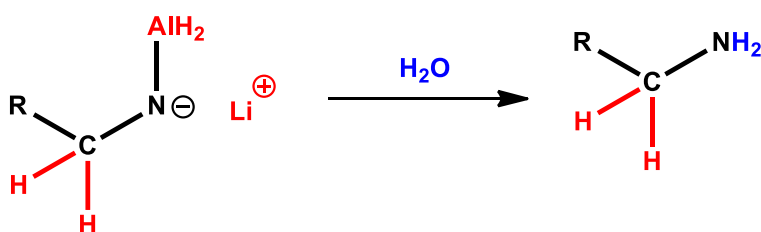
Aldehyde

Primary alcohol

Amides

Reduction of amides with $LiAlH_4$ initially produces an imine intermediate, which then undergoes further reduction and yields the corresponding amine.

Imine

Amine

Nitriles

Nitriles react with $LiAlH_4$ to produce the corresponding primary amines. This reaction is initiated by nucleophilic addition of hydride ion to the electrophilic carbon atom resulting in an ion anionic intermediate, which then reacts with AlH_3 to form an imine salt. Later on, further nucleophilic addition will take place whereby the hydride ion adds to the electrophilic carbon and forms an anionic intermediate.

In the final step, water is added to the anionic intermediate in order to form the corresponding primary amine.

III. 6. 3. 3. With DIBAL

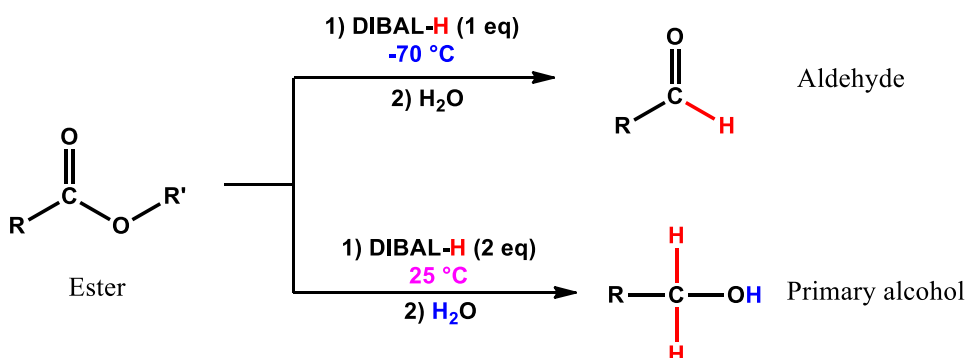
Diisobutylaluminium hydride (DIBAL) is a strong bulky reducing agent mostly used for partial reduc tion of esters to aldehydes. Moreover, it can also reduce nitriles and other carbonyl compounds. However, partial reduction with DIBAL can only be accomplished when using one molecular equivalent and at low temperature.

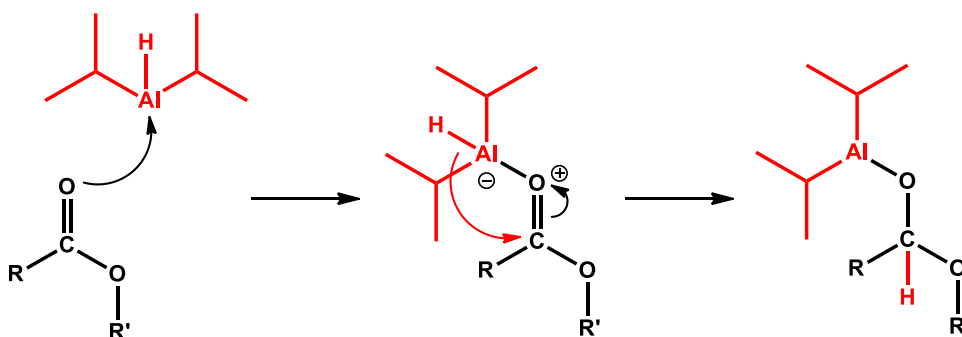
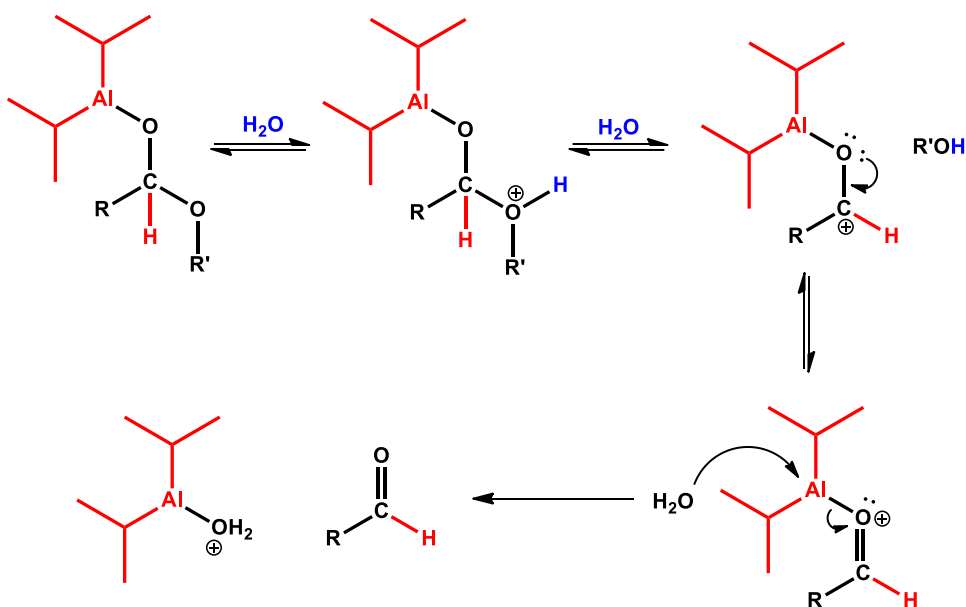
1) DIBAL-H (1 eq)
-70 °C
2) H_2O

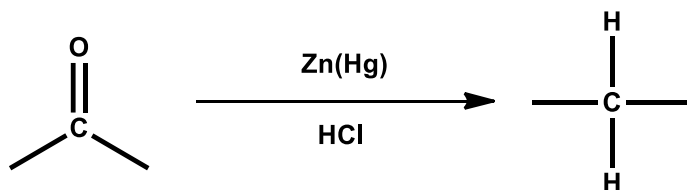
Aldehyde

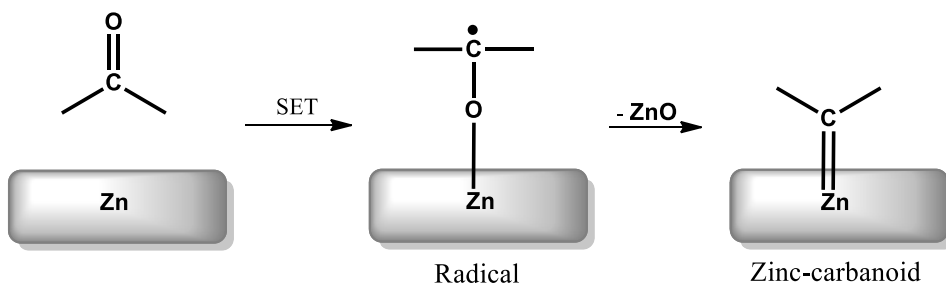
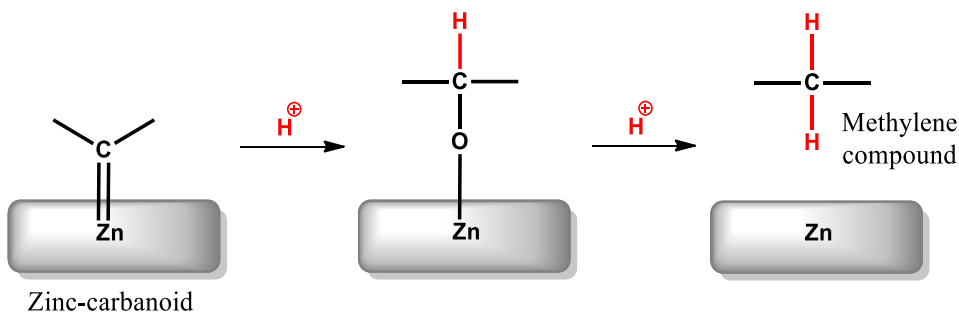
Ester

1) DIBAL-H (2 eq)
25 °C
2) H_2O

Primary alcohol

Reduction of Esters

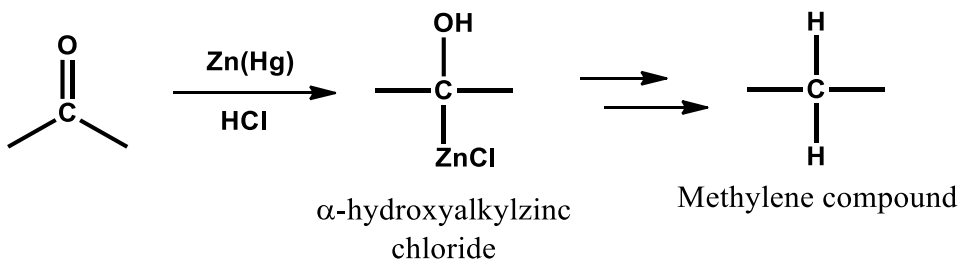
Reduction of esters to aldehydes with DIBAL must be carried out at low temperature in order to prevent the aldehydes formed from further reduction.

III. 6. 3. 4. Clemmensen Reduction (Aldehydes and Ketones)

Clemmensen reduction is a chemoselective reaction named after the Danish chemist *Eric Christian Clemmensen* . It consists in converting carbonyl group of aldehydes and ketones into methylene and it involves zinc amalgam and concentrated hydrochloric acid.

Mechanism

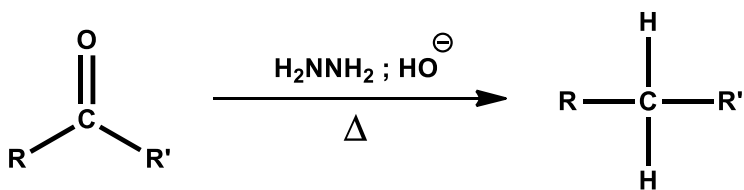
Although there is no general mechanism for Clemmensen reduction yet, chemist suggest that it proceeds by a sequence of single electron and proton transfer reactions. Initially, the carbonyl carbon of the substrate receives a single electron from zinc amalgam resulting in a radical species, which then reacts with zinc to form a zinc-carbenoid species.

Finally, a methylene product forms upon subsequent addition of protons.

Moreover, chemists have suggested another mechanism that involves α–hydroxyalkylzinc chloride intermediate.

O
C
Zn(Hg)
HCl
OH
C
ZnCl
H
C
H

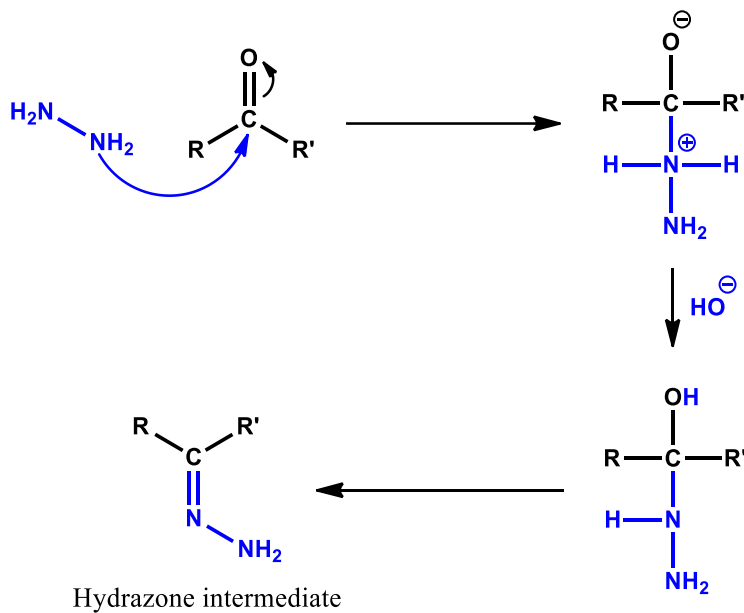
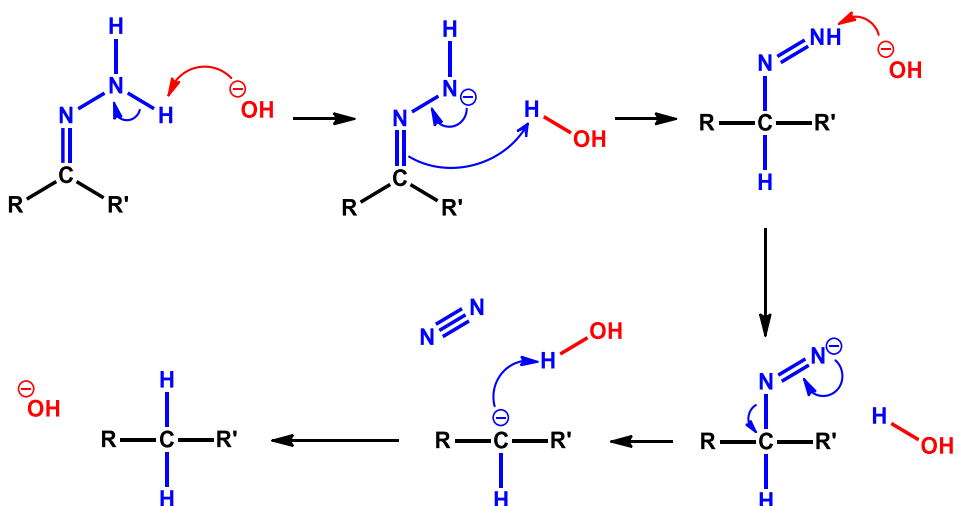
α-hydroxyalkylzinc chloride

Methylene compound

III. 6. 3. 5. Wolff–Kishner Reduction (Aldehydes and Ketones)

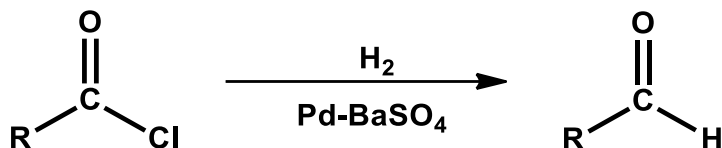
Wolff-Kishner reaction is an alternative to Clemmensen reduction named after the German chemist *Ludwig Wolff*, and the Russian chemist *Nikolai Kishner*. This reaction is mainly used when the substrate contains functional groups that are vulnerable to acidic condition. Wolff -Kishner reduction is carried out with hydrazine in basic conditions, usually with NaOH or KOH, at high temperature.

O
C
R R'
H_2NNH_2 ; $HO^{\ominus}$
Δ
H
R C R'
H

Mechanism

Wolff-Kishner reduction of aldehydes and ketones proceeds in two steps. Initially, hydrazine reacts with the carbonyl compound and forms hydrazone.

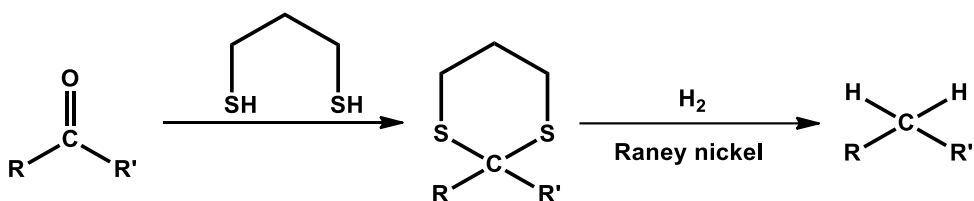
Hydrazone intermediate

The next step consists in eliminating nitrogen gas under basic condition.

III. 6. 3. 6. Rosenmund Reduction

Named after the German chemist *Karl Wilhelm Rosenmund*, Rosenmund reduction is a chemoselective reaction that converts acyl chlorides into their corresponding aldehydes using palladium on barium sulfate catalyst.

$$R-C(=O)-Cl \xrightarrow[Pd\text{-}BaSO_4]{H_2} R-C(=O)-H$$

Rosenmund reduction is typically a catalytic hydrogenation that involves gaseous hydrogen and poisoned palladium catalyst known as Rosenmund catalyst ($Pd–BaSO_4$). In this case, barium sulfate plays a crucial role in reducing palladium reactivity so it does not over reduce the aldehyde formed into a primary alcohol. Nevertheless, some acyl chlorides are highly reactive that they require a more poisoned catalyst, which can be prepared by addition of thioquinanthrene or thiourea.

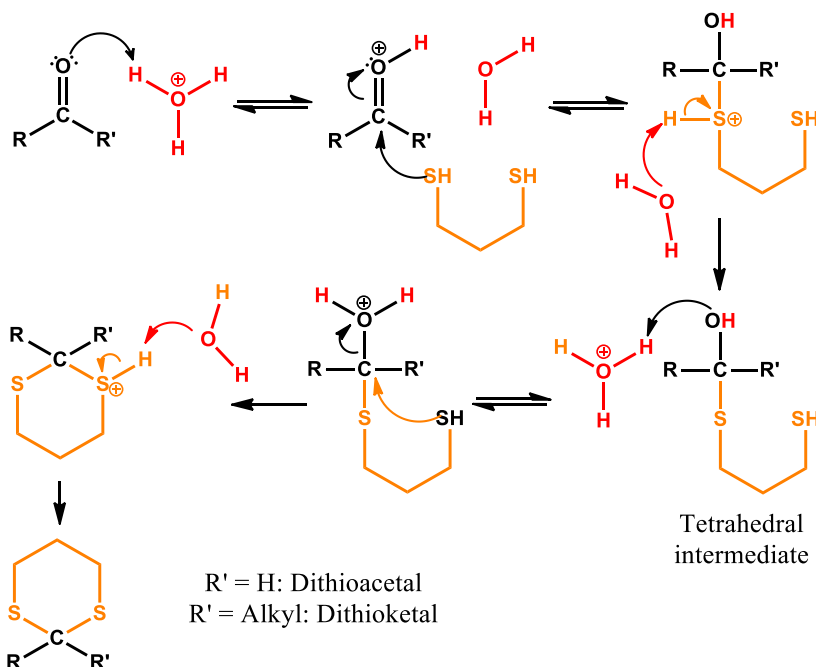
III. 6. 3. 7. Mozingo Reduction

Mozingo reduction is a chemoselective reaction that reduces aldehydes and ketones to their corresponding methylene compounds. This reaction is named after the chemist *Ralph Mozingo* and it involves a dithioacetal intermediate.

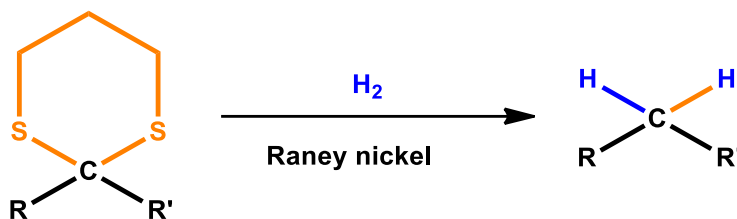
$$R-C(=O)-R' \xrightarrow{HS-CH_2CH_2CH_2-SH} \text{1,3-dithiane } (R, R') \xrightarrow[\text{Raney nickel}]{H_2} R-CH_2-R'$$

Mechanism

Mozingo reduction is a two-steps reaction that involves dithioacetal or dithioketal intermediate. Initially, dithiol reacts with the carbonyl compound to give dithioacetal or dithioketal. This reaction is similar to the formation of ketals and acetals.

R' = H: Dithioacetal
R' = Alkyl: Dithioketal

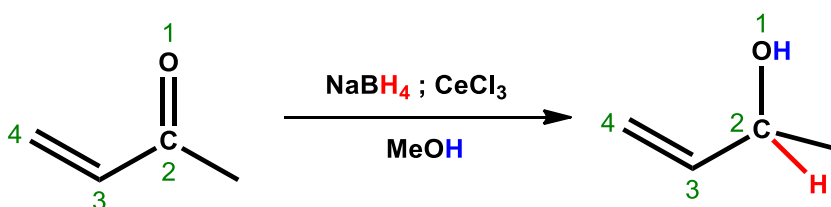
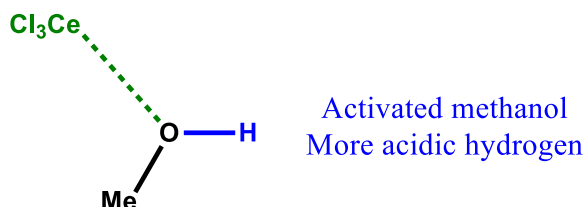
Tetrahedral intermediate

The next steps consists in catalytic hydrogenation of the dithioacetal/dithioketal intermediate, which is carried out with gaseous hydrogen and Raney nickel catalyst.

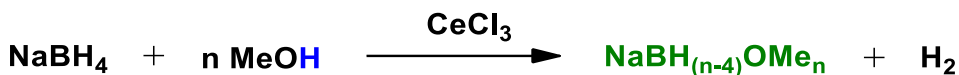
H_2

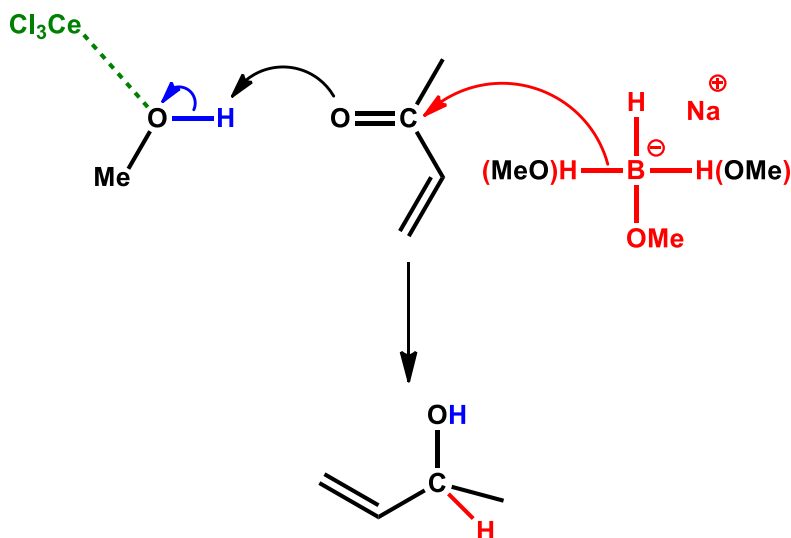
Raney nickel

III. 6. 3. 8. Luche Reduction

Luche reduction is a regioselective reaction that converts α, β–unsaturated ketones into allylic alcohols. This reaction involves sodium borohydride and a lanthanide trichloride catalyst usually cerium trichloride $CeCl_3$ in the presence of an alcohol such as MeOH.

$NaBH_4$; $CeCl_3$

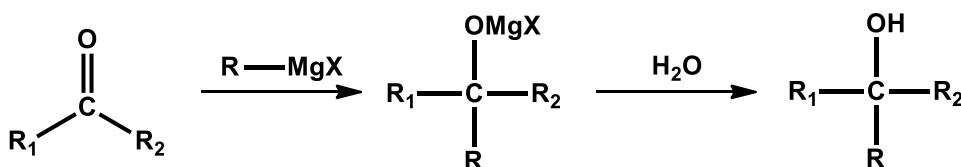
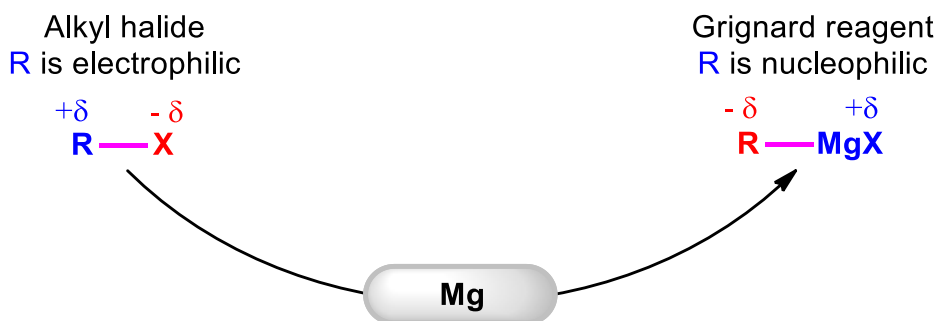
MeOH

In this reaction, cerium trichloride $CeCl_3$ plays a significant role in regiochemistry. Initially, it activates the alcohol used in the reaction by making its proton more acidic and hence, more susceptible for nucleophilic attacks.

Later on, the activated alcohol reacts with sodium borohydride and generates a harder reducing agent that is able to perform 1,2-addition on carbonyl group.

$$NaBH_4 + n\ MeOH \xrightarrow{CeCl_3} NaBH_{(n-4)}OMe_n + H_2$$

Mechanism

Luche reduction is a one-step reaction whereby a hydride ion attacks the carbonyl carbon at the same time the oxygen atom abstracts a hydrogen proton from the activated methanol resulting in an allylic alcohol.

IV. Selection of Named Reactions

IV. 1. Grignard Reaction

Grignard reaction is a very important reaction in organic synthesis that consists in adding an organomagnesium compound known as Grignard reagent to a polarized multiple bond. Moreover, although Grignard reaction is suitable for several compounds such as aldehydes, ketones, esters, carbon dioxide, and nitriles, it is mostly used to synthesize alcohols from aldehydes and ketones.

$$R_1-C(=O)-R_2 \xrightarrow{R-MgX} R_1-C(OMgX)(R)-R_2 \xrightarrow{H_2O} R_1-C(OH)(R)-R_2$$

Grignard reagent can be prepared by reacting an alkyl or aryl halide with metal magnesium. This reaction takes place at the surface of the metal where a single electron is transferred from magnesium to the alky halide, or aryl halide resulting in an organomagnesium compound. The purpose of preparing Grignard reagent is generating a nucleophile by reversing the formal charge of the hydrocarbon residue from a positive formal charge in the starting material to a negative formal charge in the final product.

Mechanism

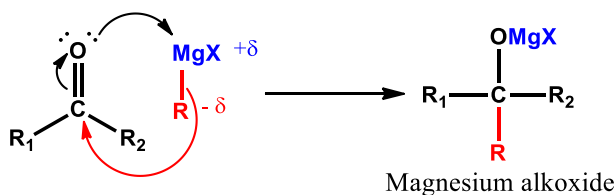
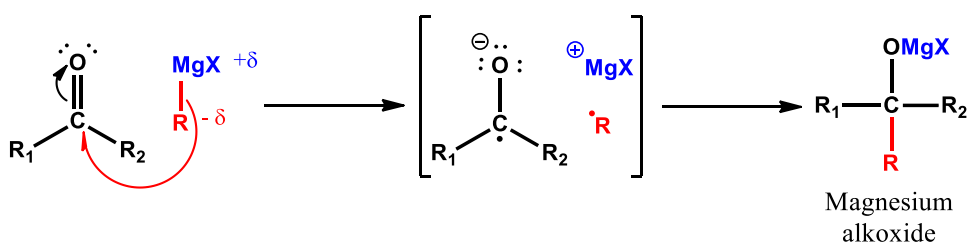
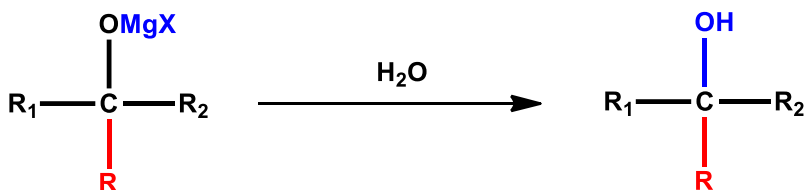
Grignard reaction is usually carried out with a nucleophilic solvent such as ether, diethyl ether, or THF and it proceeds in two steps. For aldehydes and ketones, two different mechanisms are proposed for the first step. A polar mechanism, which involves concerted addition of Grignard reagent to the carbonyl group, and the radical mechanism, which proceeds via single-electron-transfer from Grignard

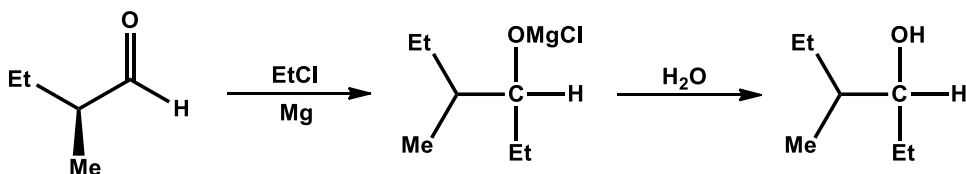
reagent to the carbonyl group. In both cases, a magnesium alkoxide intermediate is formed.

Polar mechanism

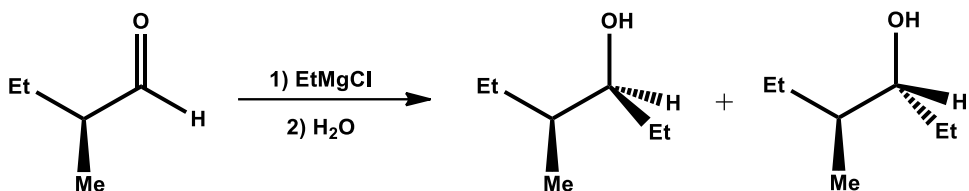
Magnesium alkoxide

Radical mechanism

Magnesium alkoxide

The next step involves a hydrolysis workup wh ereby the corresponding alcohol forms.

➲ ***Example***

Preparation of alcohol from (*S*)-2-methylbutanal.

Note that ethyl group can add to the carbonyl carbon from either sides, which leads to the formation of two diastereoisomers.

1) EtMgCl

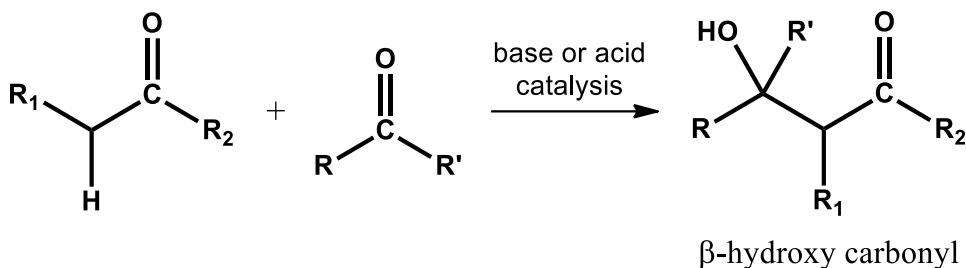
2) H_2O

The following table shows how different product react with Grignard reagent.

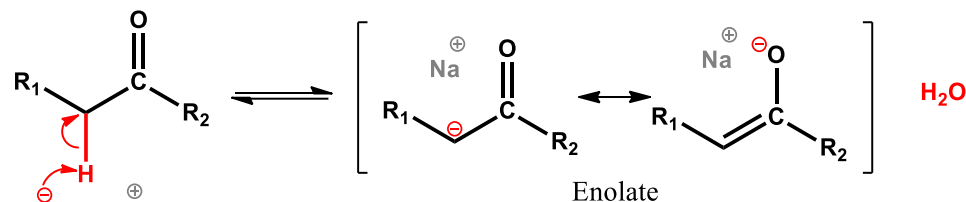
Substrate		Product
R_1CHO	1) RMgX 2) H_2O	$R-C(OH)(H)-R_1$
R_1COR_2	1) RMgX 2) H_2O	$R_1-C(OH)(R_2)-R$
R_1COOH	RMgX	$R_1COO^{\ominus}$ $^{\oplus}MgX$ RH
R_1COCl	1) RMgX 2) H_2O	$R-C(OH)(R)-R_1$
R_1COOR_2	1) RMgX 2) H_2O	$R-C(OH)(R)-R_1$
CO_2	1) RMgX 2) H_2O	$RCOOH$
$R_1-C\equiv N$	1) RMgX 2) H_2O	R_1COR

IV. 2. Aldol Reaction

Aldol reaction is a frequently used reaction in organic chemistry whereby two carbonyl compounds that can be aldehydes or ketones, combine to form β–hydroxy aldehyde (aldol) or β–hydroxy ketone (ketol).

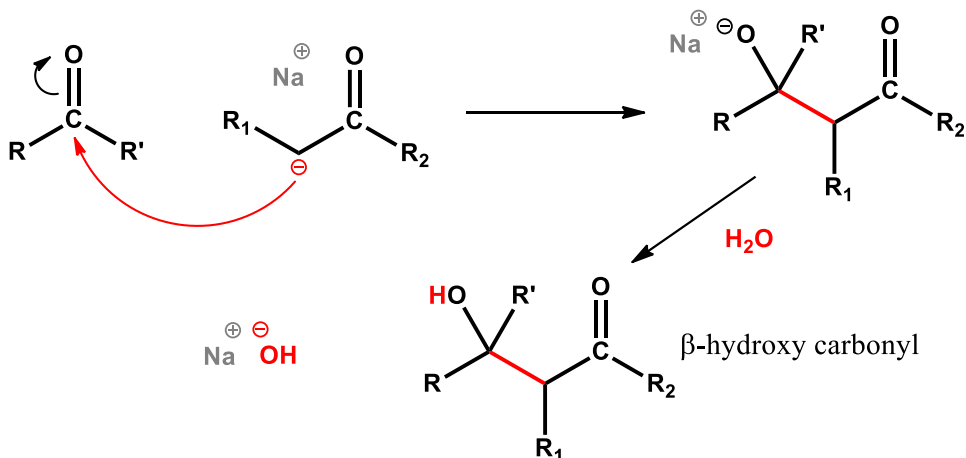
base or acid catalysis

β-hydroxy carbonyl

This reaction requires a carbonyl compound that contains at least one α–hydrogen atom and it proceeds in two reversible steps. The first step is usually performed with a basic catalyst such as NaOH, or KOH, which deprotonates the enolizable carbonyl in order to form an enolate.

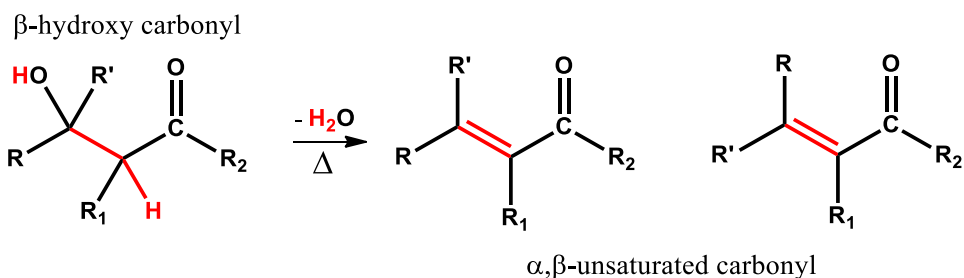
H_2O

Enolate

The second step is characterized by the nucleophilic addition of the enolate to the electrophilic carbonyl carbon of another molecule leading to the formation of β–hydroxy carbonyl compound.

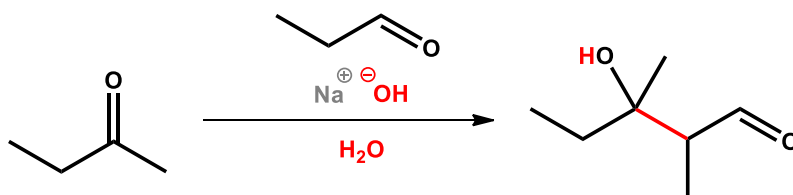
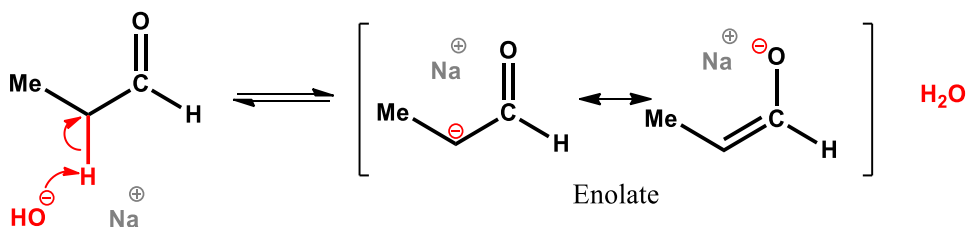
H_2O

β-hydroxy carbonyl

If the resulting β–hydroxy carbonyl compound still has another α–hydrogen atom, a dehydration reaction can take place at high temperature leading to the formation of α, β–unsaturated carbonyl compound. In this case, the overall reaction is called *aldol condensation reaction.*

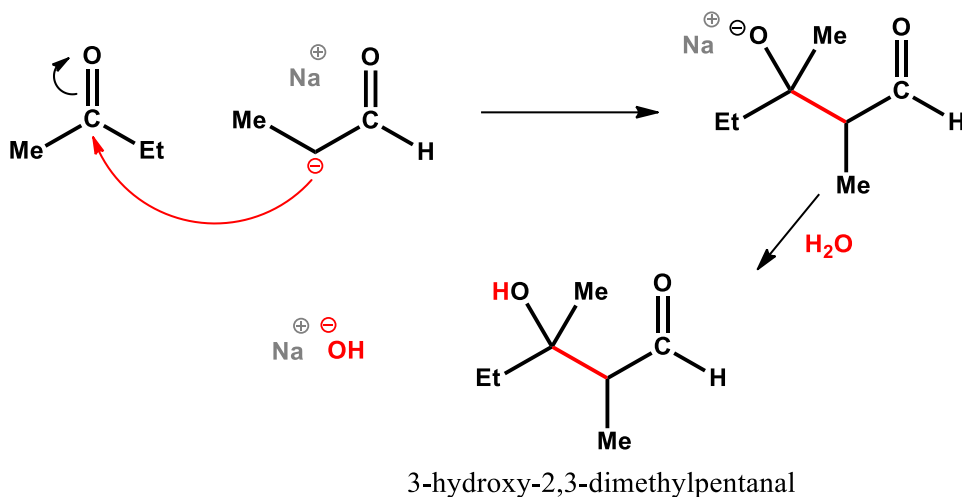
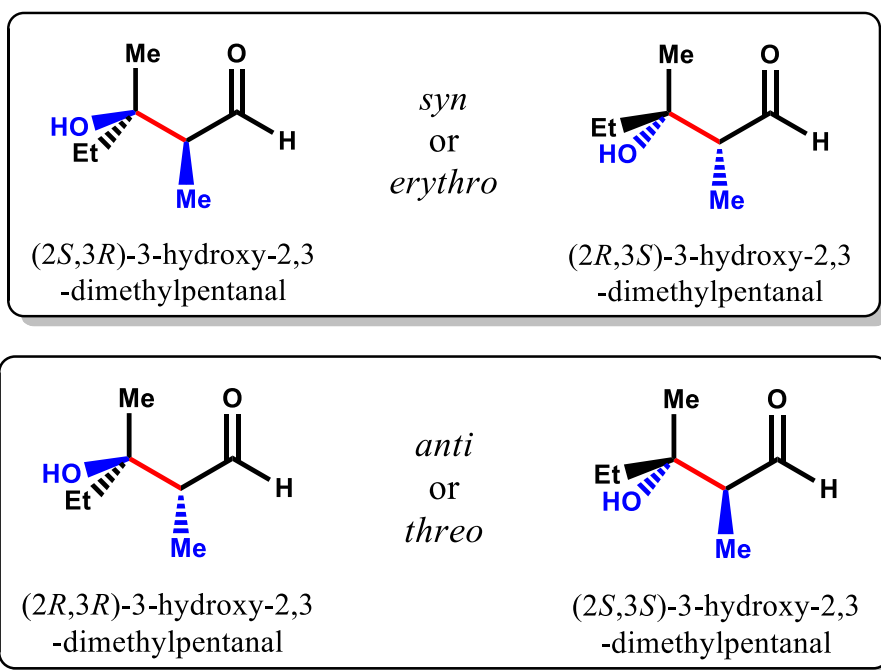
β-hydroxy carbonyl

α,β-unsaturated carbonyl

In general, aldol reaction yields a mixture of products. If two identical aldehydes are invo lved, the equilibrium shifts to product. In contrast, when two identical ketones react, the equilibrium shifts to the left. As a result, the reaction conditions must be adjusted in order to obtain a better yield. Moreover, aldol reaction of two unsymmetrical ketones having α–hydrogen atoms at both sides yields a mixture of compounds. Nevertheless, the reacti on is more likely to take place at the least hindered α–carbon atom.

➲ ***Example***

Aldolisation of butan-2-one with propionaldehyde.

Initially, propionaldehyde is treated with NaOH in order to produce the corresponding enolate intermediate.

Enolate

Later on, the enolate would attack the electrophilic carbonyl carbon of the butan-2-one resulting in an anionic tetrahedral intermediate, which then gets protonated to form 3-hydroxy-2,3-dimethylpentanal.

3-hydroxy-2,3-dimethylpentanal

In this case, because the enolate can add to the carbonyl carbon from either side, the reaction would give two diastereomeric pairs of enantiomers.

IV. 3. Michael Reaction

Named after the American chemist *Arthur Michael*, Michael reaction, also known as Michael addition, is a nucleophilic conjugate addition of a **Michael donor** to a **Michael acceptor** in order to produce Michael adduct in the presence of a base.

EWG EWG — Michael donor; EWG — Michael acceptor; Base →; EWG, EWG, EWG — Michael adduct

Michael donors are active me thylene compounds, which form good nucleophiles upon treatment with a base. Michael acceptor, on the other hand, are α,β–unsaturated active olefins, which act as electrophiles by accepting electrons from a Michael donor species.

Pentane-2,4-dione

Malononitrile

Diethyl malonate

Dinitromethane

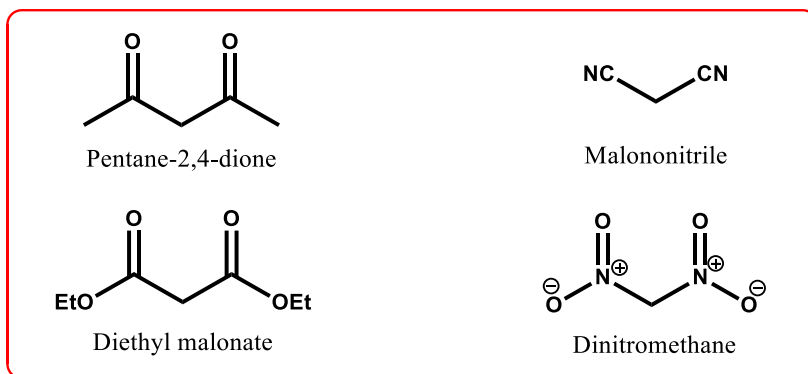
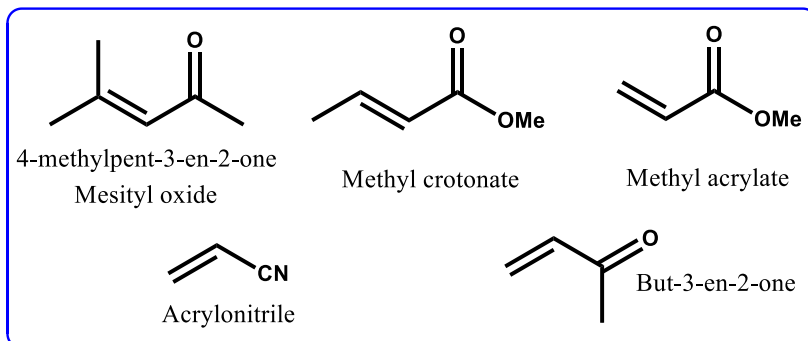
Michael donor

4-methylpent-3-en-2-one
Mesityl oxide

Methyl crotonate

Methyl acrylate

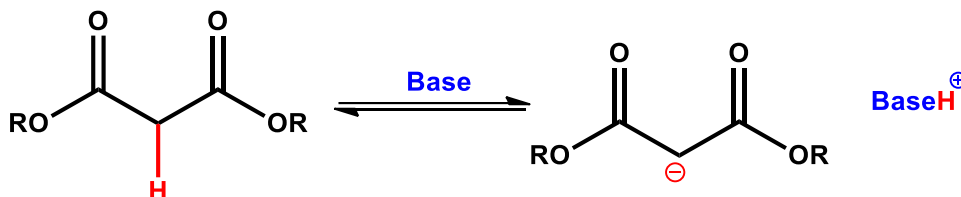
Acrylonitrile

But-3-en-2-one

Michael acceptor

Mechanism

Michael addition is performed under basic conditions and it proceeds in two steps. Initially, a base abstracts the acidic hydrogen from the Michael donor to produce a resonance stabilized carbanion species.

Base

BaseH

Later on, the Michael donor "nucleophile" attacks the Michael acceptor "electrophile" at the β–position resulting in the corresponding Michael adduct.This nucleophilic attack is termed *conjugated nucleophilic addition.*

Michael acceptor

Michael donor

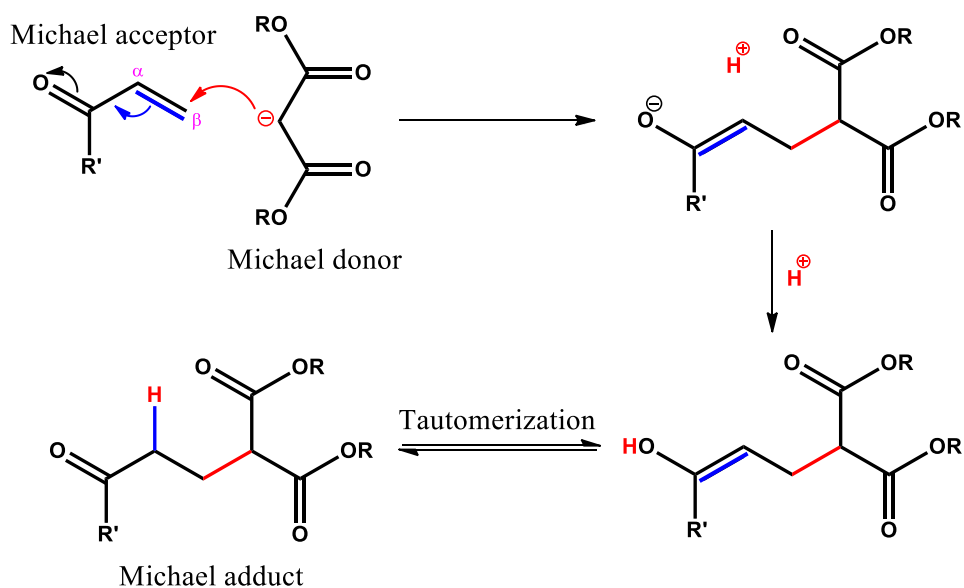
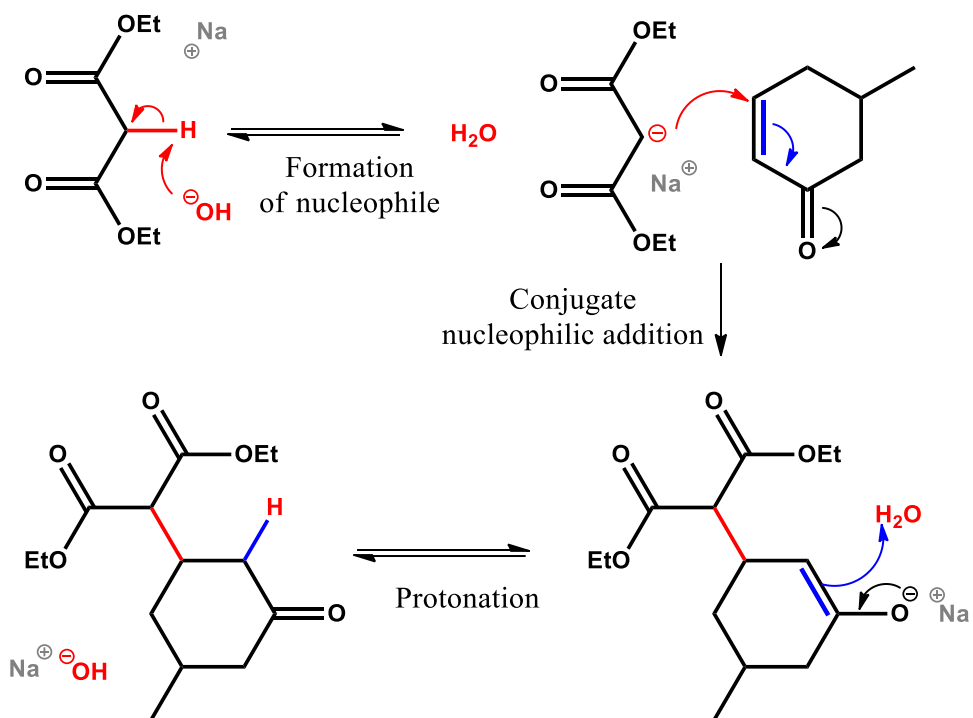
Tautomerization

Michael adduct

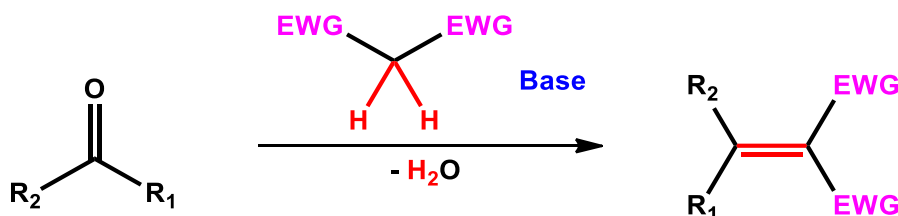
➲ ***Example***

Formation of nucleophile

Conjugate nucleophilic addition

Protonation

IV. 4. Knoevenagel Reaction

Named after the German chemist *Heinrich Emil Albert Knoevenagel*, Knoevenagel reaction, also known as Knoevenagel condensation, is the reaction of an aldehyde or ketone with an active methylene compound in the presence of a weak basic catalyst. This particu lar reaction usually produces an α, β–unsaturated carbonyl compound.

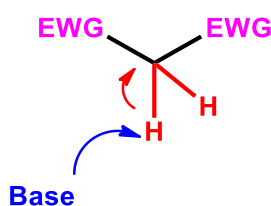
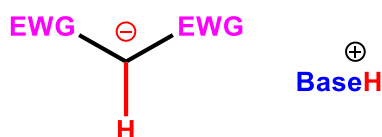
EWG EWG
H H
Base
O
R2 R1
- H_2O
R2 EWG
R1 EWG

Mechanism

The first step of Knoevenagel reaction involves deprotonation of the active methylene compound, which leads to the formation of a stable carbanion species "nucleophile". This process can be achieved by a catalytic amount of a wea k organic base such as amines.

Active methylene compound

Carbanion intermediate

EWG EWG
H
H
Base

EWG ⊖ EWG
H
⊕
BaseH

In the next step, the nucleophile "carbanion" would attack the electrophilic carbonyl carbon "substrate" resulting in anionic intermediate, which then gets protonated. At this point, if another α–hydrogen is present, an elimination reaction would take place whereby an α, β–unsaturated compound is formed.

Nucleophilic addition

Protonation

$BaseH^{\oplus}$

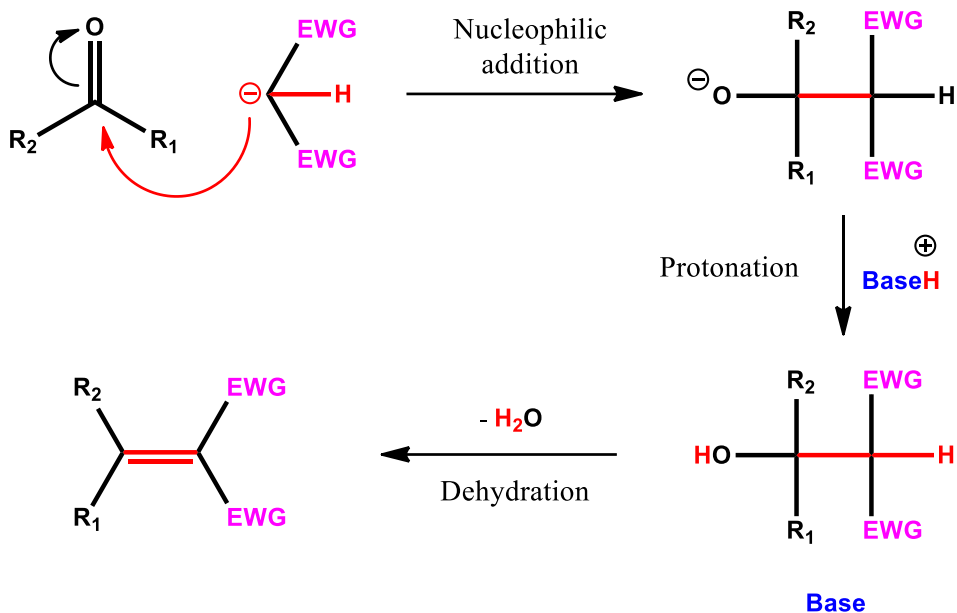
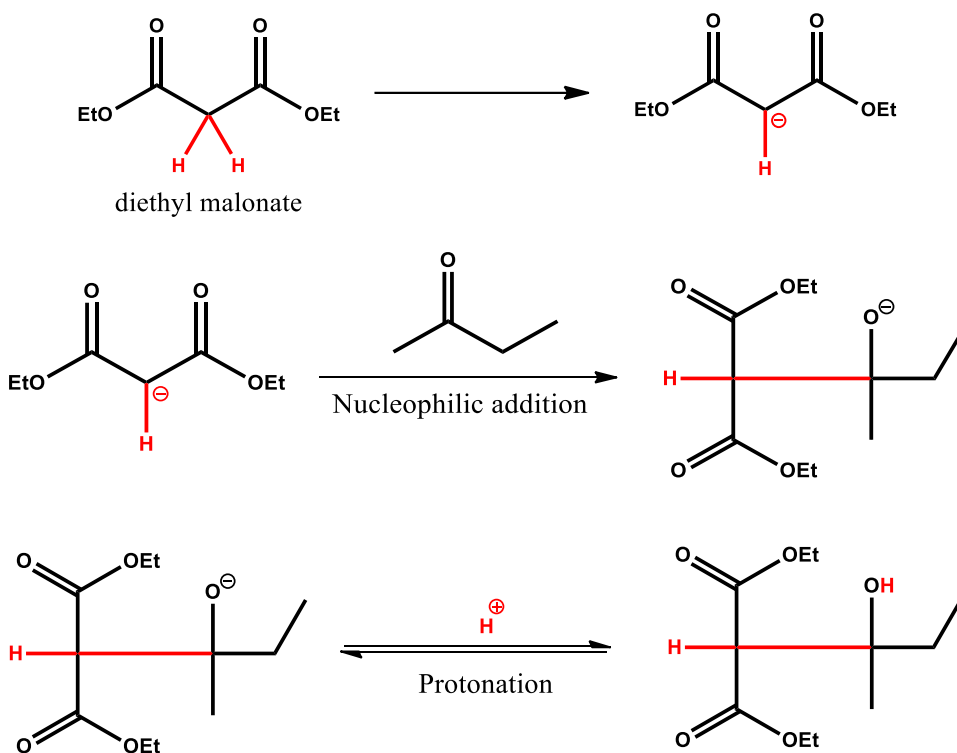
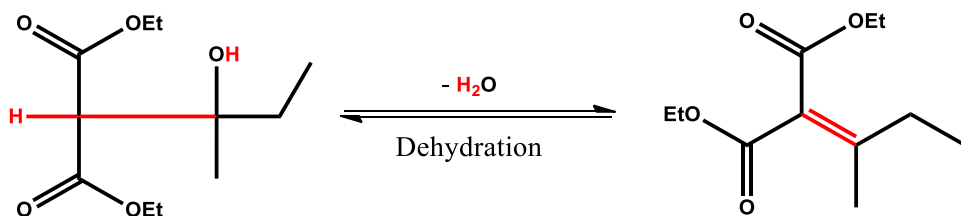
$- H_2O$

Dehydration

Base

➲ ***Example***

- H_2O

Dehydration

➲ ***Example***

In case of malonic acid , Knoevenagel condensation often involves subsequent decarboxylation of the dicarboxylic acid formed often occurs.

Nucleophilic addition

Protonation

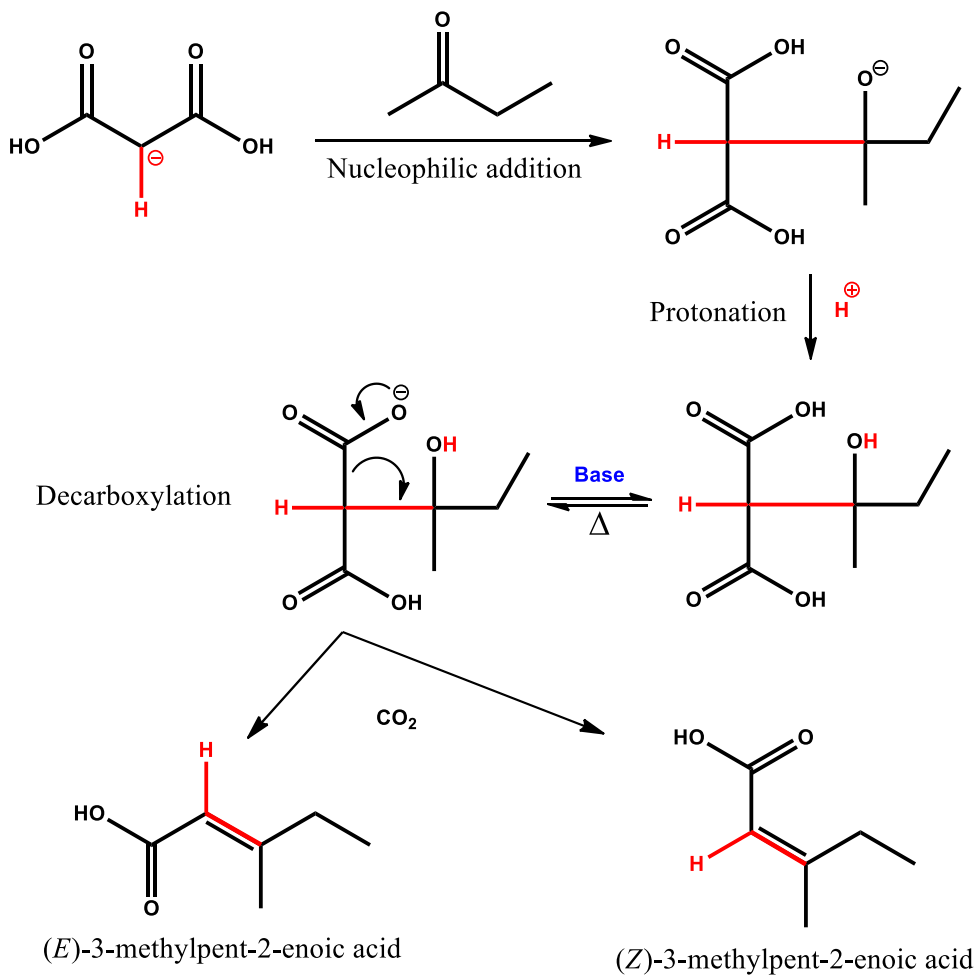
Decarboxylation

Base

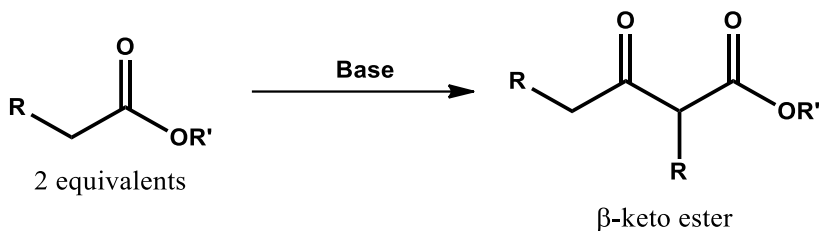
Δ

CO_2

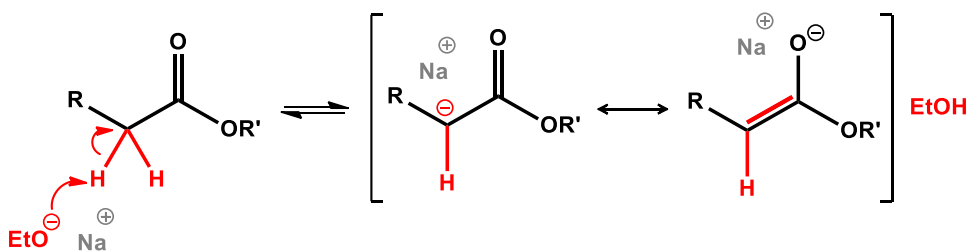
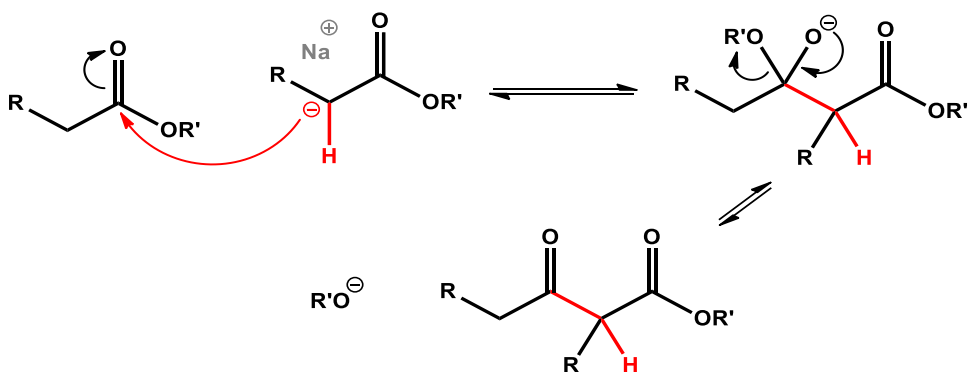
(*E*)-3-methylpent-2-enoic acid

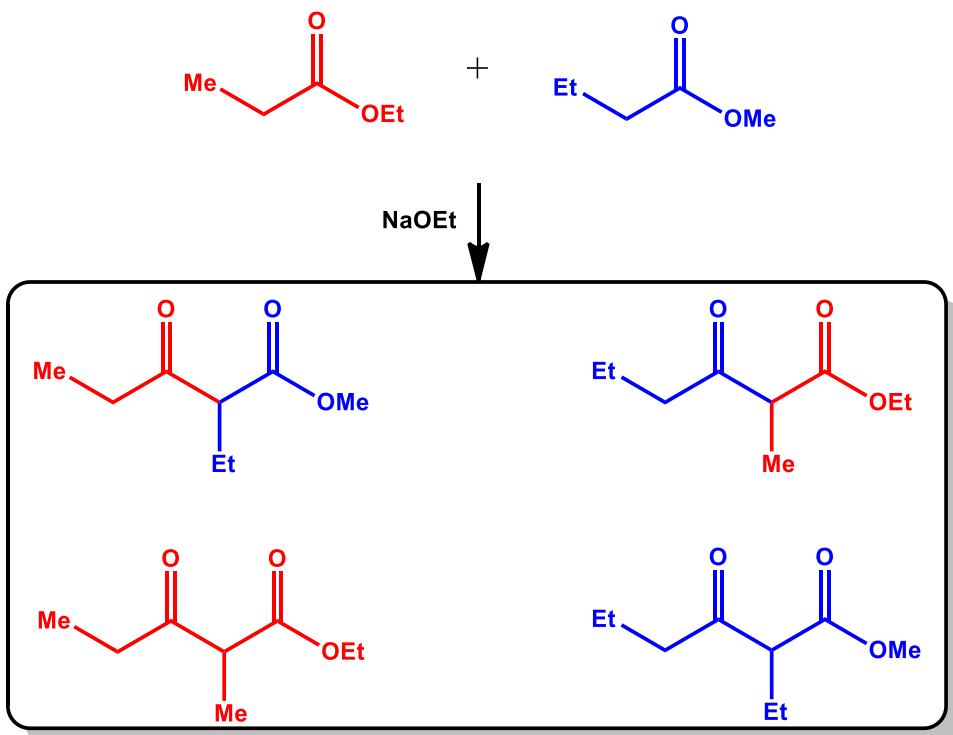
(*Z*)-3-methylpent-2-enoic acid

IV. 5. Claisen Reaction

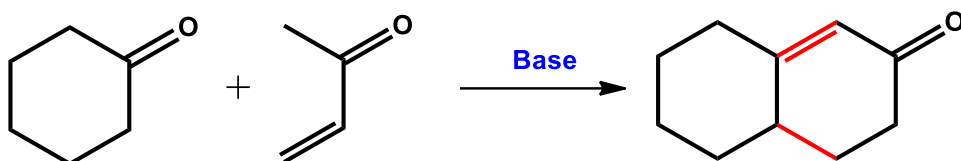
Named after the German chemist *Ludwig Rainer Claisen* , Claisen reaction, also known as acetoacetic ester condensation , is the condensation of two carboxylic esters upon treatment with a strong base to produce a β–keto ester compound.

R–CH2–C(=O)–OR' (2 equivalents) —Base→ R–CH2–C(=O)–CH(R)–C(=O)–OR' (β-keto ester)

Mechanism

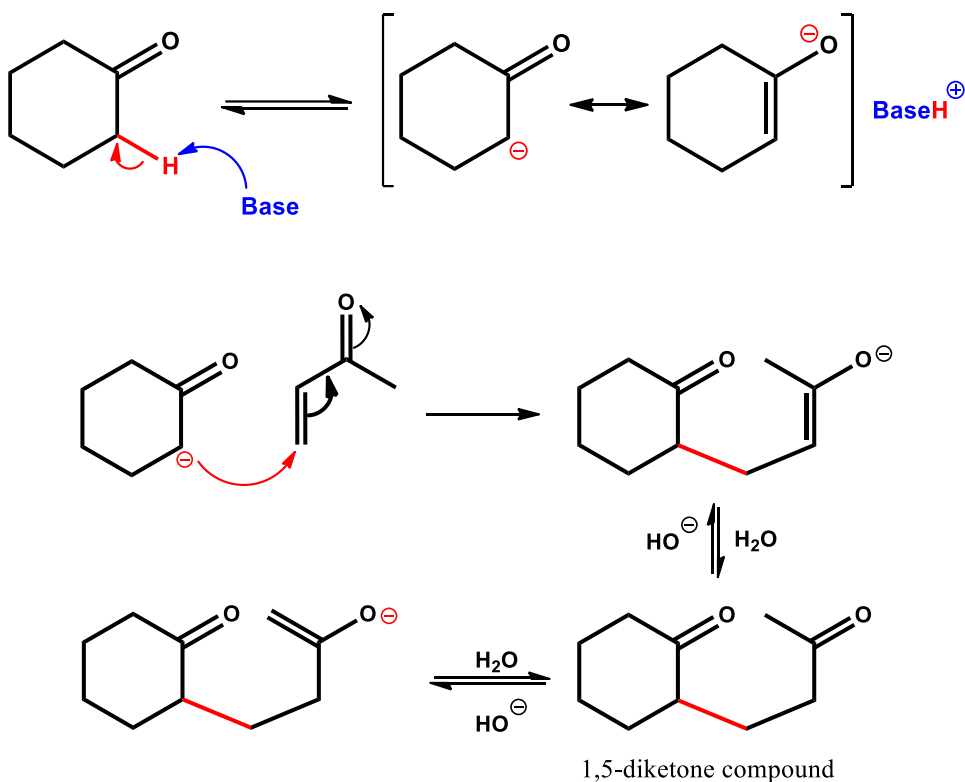
Claisen reaction requires carboxylic esters that contain two α–hydrogens and proceeds in two reversible steps. Initially, a strong base such as ethoxide abstracts one α–hydrogen proton from the carboxylic ester resulting in an anionic intermediate.

EtO⊖ Na⊕ + R–CH2–C(=O)–OR' ⇌ [Na⊕ R–CH⊖–C(=O)–OR' ⟷ Na⊕ R–CH=C(O⊖)–OR'] + EtOH

The next step is characterized by the nucleophilic addition of the anionic intermediate to the electrophilic carbon of another carboxylic ester molecule. At this point, a tetrahedral anionic intermediate forms, which then collapses into a β–keto ester compound after the elimination of the alkoxy group $R'O^{-}$.

In addition, when two asymmetrical carboxylic ester s are involved, the reaction would yield a mixture of β–keto ester compounds.

➲ ***Example***

IV. 6. Robinson Annulation

Named after the British chemist *Robert Robinson*, Robinson annulation is a cyclization reaction to create a six membered ring by forming three carbon–carbon bonds. This particular reaction is widely used in the synthesis of terpenes, and steroids.

Mechanism

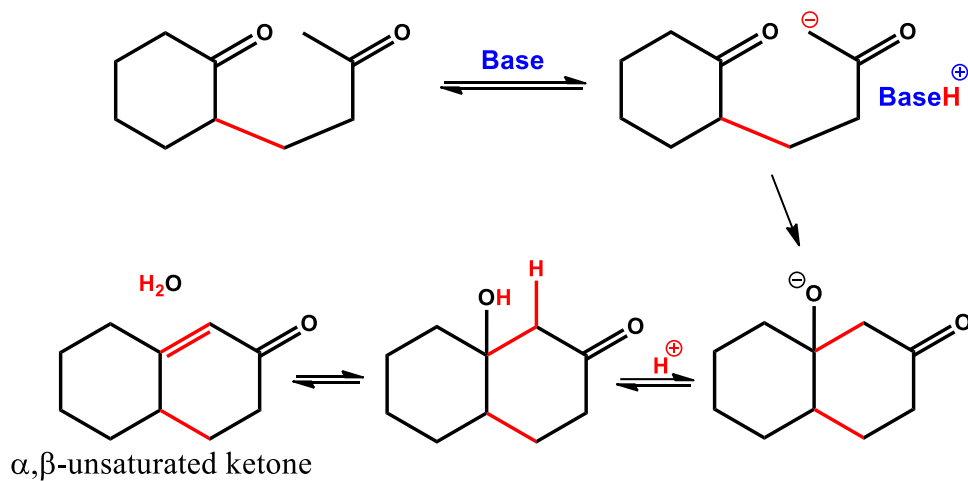
Robinson annulation is carried out under basic condition s and it proceeds in two stages. Initially, Michael addition takes place between a cyclic ketone and a Michael acceptor, which gives a 1,5-diketone compound.

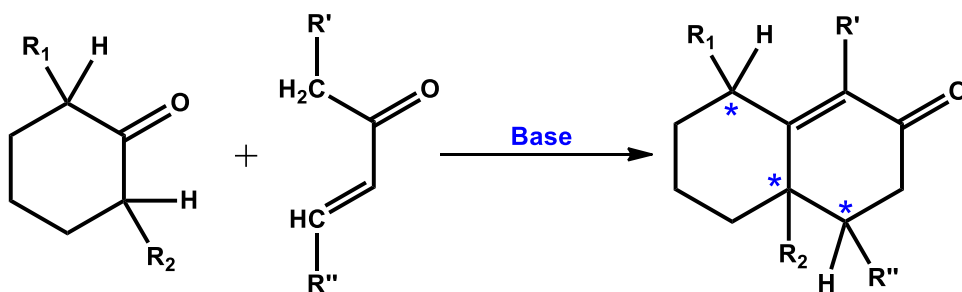
1,5-diketone compound

The second reaction is an interamolecular aldol condensation whereby the 1, 5 - diketone compound converts into an α, β–unsaturated ketone.

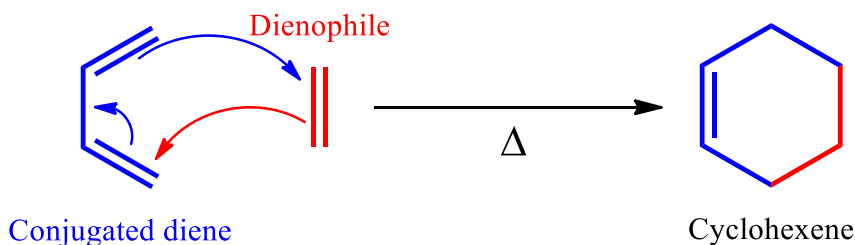
Base

BaseH

H_2O

α,β-unsaturated ketone

In terms of ste reochemistry, Robinson annulation can yield a mixture of stereoisomers since the final product may have new stereocenters.

Base

IV. 7. Diels-Alder Reaction

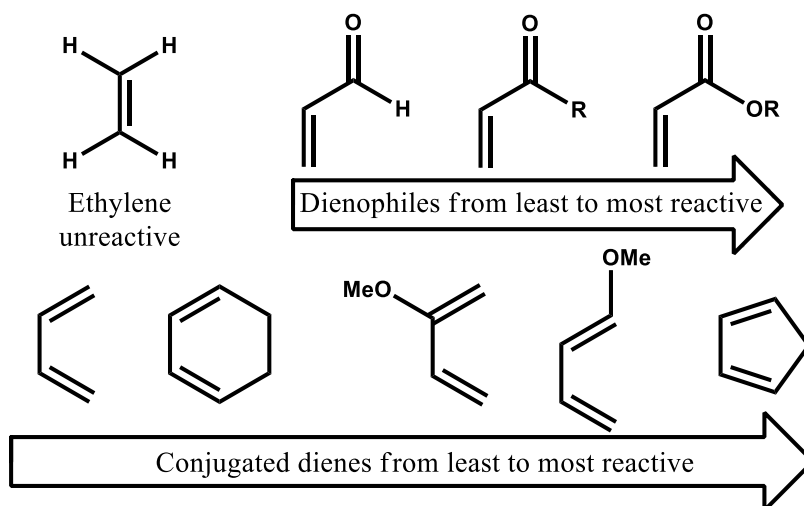
Named after the German chemists *Kurt Alder* and *Otto Paul Hermann Diels*, Diels-Alder reaction, also known as [4+2]-cycloaddition, is a concerted cyclization reaction that involves a conjugated diene and a dienophile to produce a cyclohexene compound. This particular reaction is usually thermodynamically favorable since two π bonds "weak bonds" are converted into two new σ bonds "strong bonds".

Moreover, Diels-Alder reaction is favored with dienophiles having an electron-withdrawing groups and electron releasing groups on the conjugated dienes.

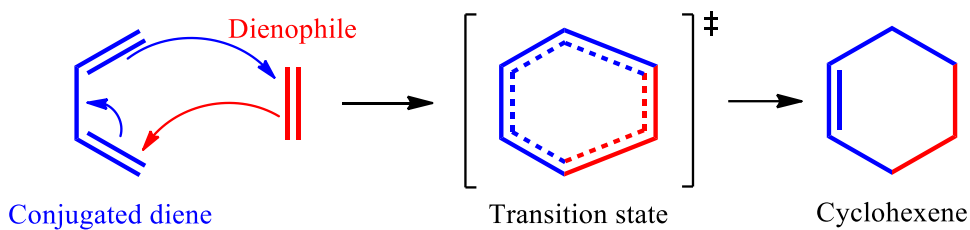
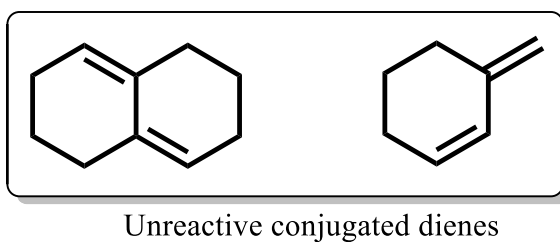
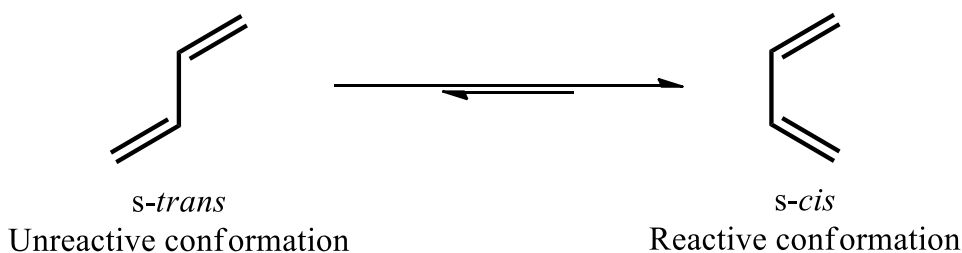
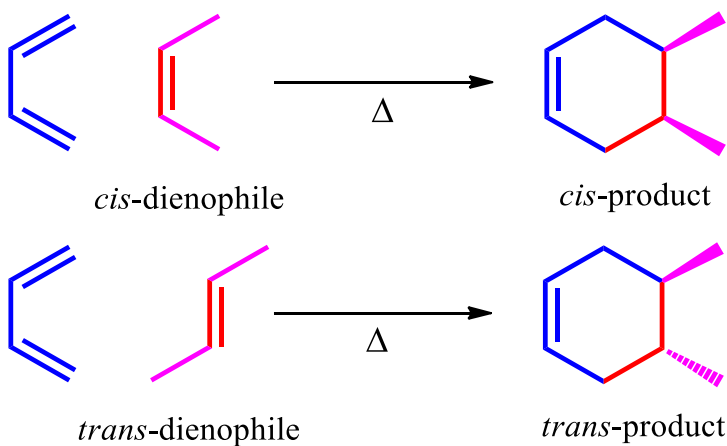
H H H H O H O R O OR

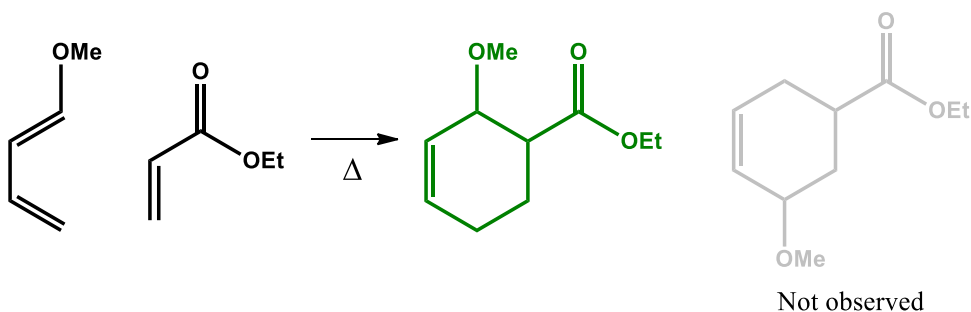
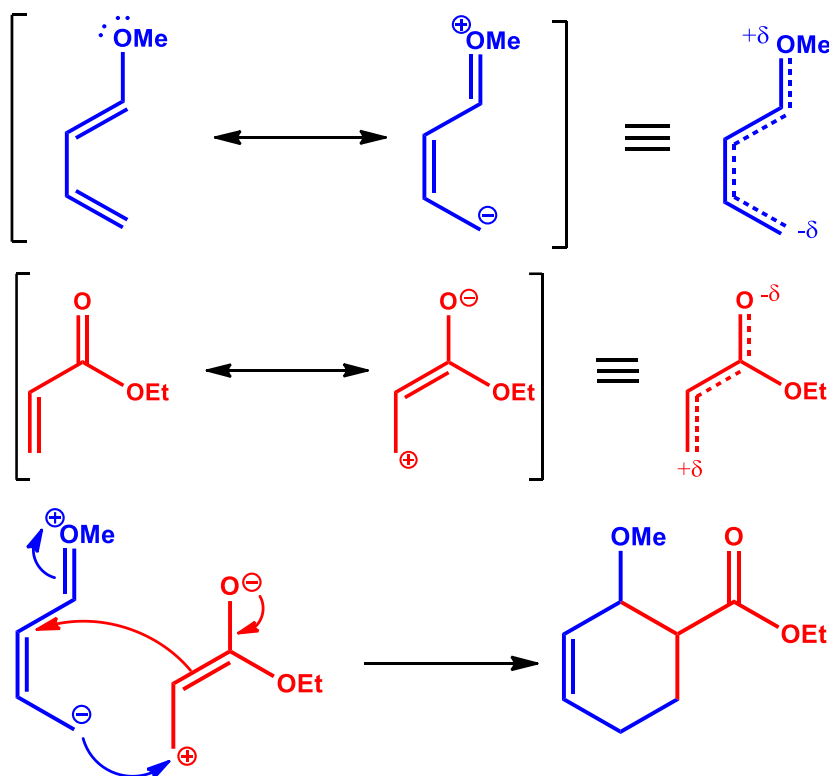
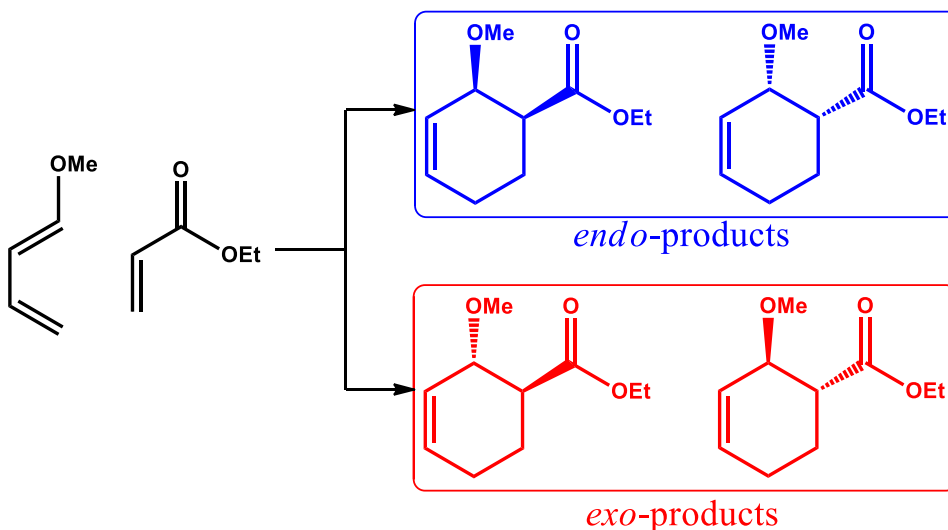
Ethylene
unreactive

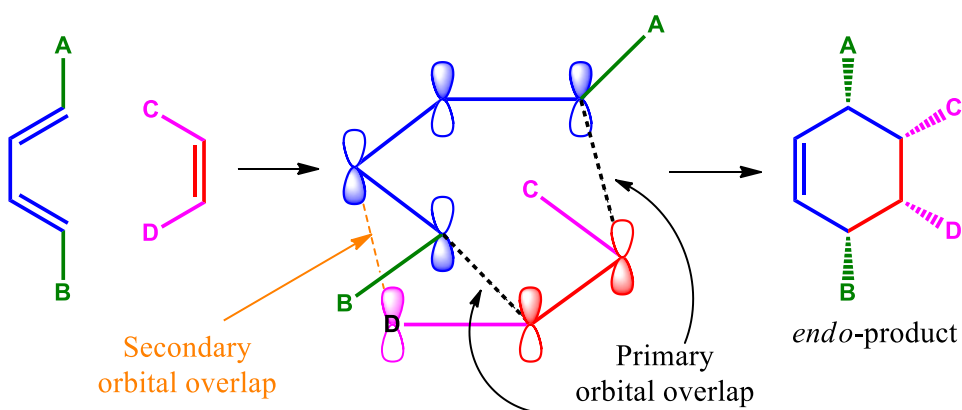
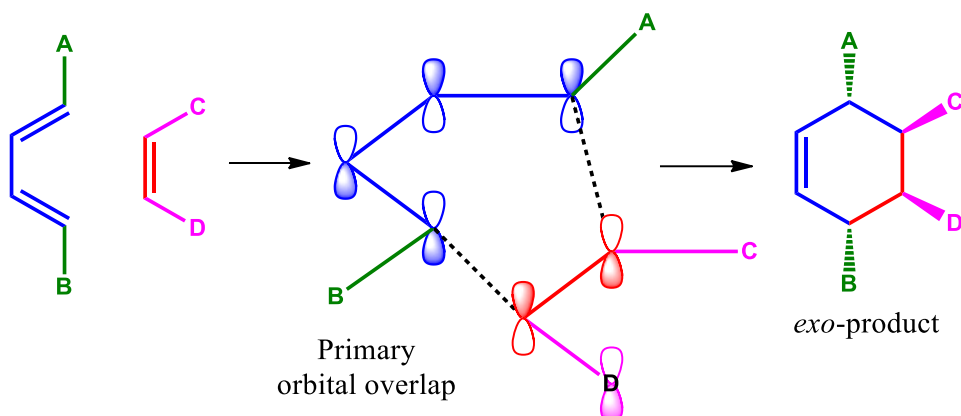
Dienophiles from least to most reactive

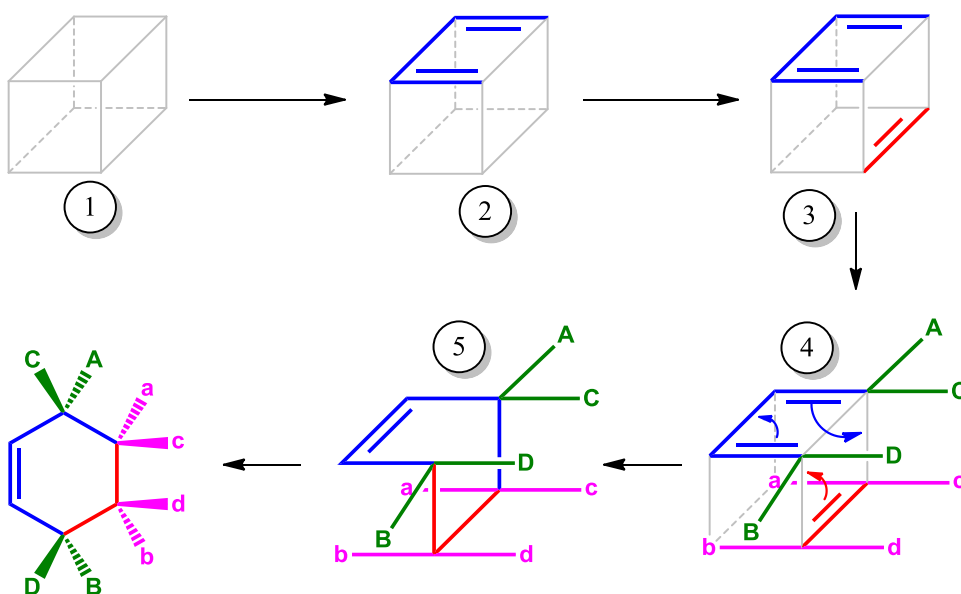
OMe MeO

Conjugated dienes from least to most reactive

Mechanism

Diels-Alder reaction is a one-step reaction where two carbon-carbon covalent bonds form simultaneously. In this reaction, the highest occupied molecular orbitals HOMO of the diene overlap with the lowest unoccupied molecular orbitals LUMO of the dienophile.

Moreover, for a Diels-Alder reaction to occur, the conjugated diene must adopt an s-*cis* configuration.

Furthermore, at the course of the reaction, the relative position of the dienophile substituents is preserved. As a result, a *cis*-dienophile gives a *cis*-product while a *trans*-dienophile yields a *trans*-product.

Diels-Alder is a **regioselective** reaction that favors certain products over the others.

Not observed

The reason behind this regioselectivity can be explained by resonance structures of reactants "dienophile and conjugated diene". For instance, the electron-rich carbon of the conjugated diene is more likely to form a single bond with the electron - deficient carbon of the dienophile.

Another aspect of Diels-Alder reaction is the stereochemistry of the final product when one terminus of either reactant is attached to at least two different groups. In this case, two types of products may be obtained; the *endo*-product, which is the thermodynamic adduct, where the π-substituents on the dienophile point towards the diene, and the *exo*-product, which is the kinetic adduct, where the π-substituents on the dienophile point away from the diene.

In general, Diels-Alder reaction favors the *endo*-product over the *exo*-product even though it is more sterically congested. The reason behind this is that in addition to the primary orbital overlap observed in the case of *exo*-product transition state, the *endo*-product also exhibits a secondary orbital overlap between the conjugated diene and the dienophile.

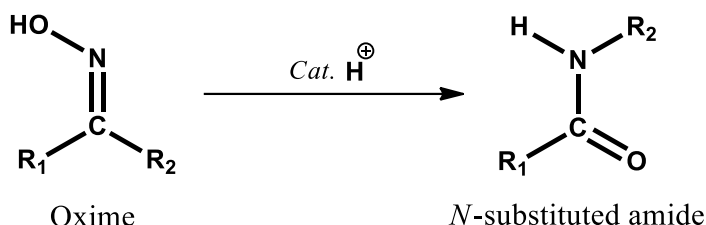
Secondary orbital overlap
Primary orbital overlap
endo-product

In order to determine the stereochemistry of the final product, the cube method can be used to visualize the relative orientation of the substituents at the course of Diels-Alder reaction.

1. Draw a cube.
2. Draw the conjugated dine on the top face of the cube.
3. Draw the dienophile on the bottom face of the cube.
4. Add the substituents attached the sp ^{2} carbons of the dienophile and the conjugated diene.
5. Draw the covalent bonds then deduce the stereochemistry of the product obtained.

IV. 8. Beckmann Rearrangement

Named after the German chemist *Ernst Otto Beckmann*, Beckmann rearrangement is a reaction whereby an oxime rearranges to an *N*-substituted amide under acidic condition. This reaction is more suitable for ketoximes since aldoximes tend to be less reactive.

Cat. $H^{\oplus}$

Oxime

N-substituted amide

Mechanism

The first step of Beckmann rearrangement involves the conversion of the oxime hydroxy group into a better leaving group. This process can be achieved by using a protic acidic catalyst, which protonates the oxime hydroxy group resulting in an oxonium intermediate. Later on, the substituent on *anti* position with respect to the leaving group would migrate to the nitrogen atom as a water molecule gets removed, leading to the formation of a cationic intermediate. At this point, a water molecule would capture the carbocation to form an iminol, which then tautomerizes to a more stable amide tautomer.

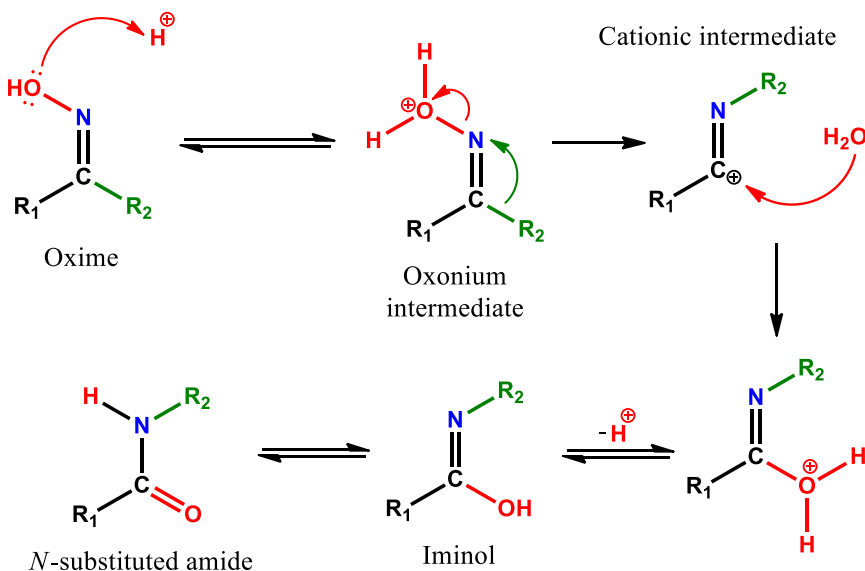
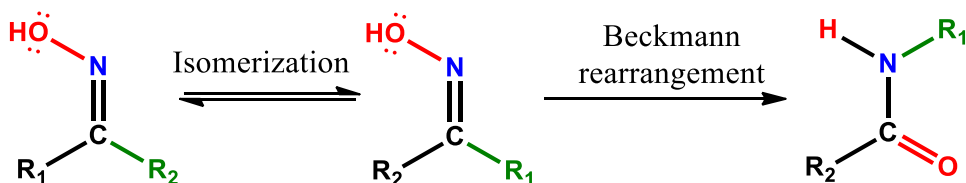
Cationic intermediate

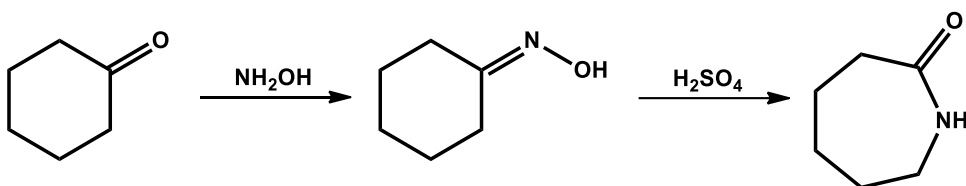
Oxime

Oxonium intermediate

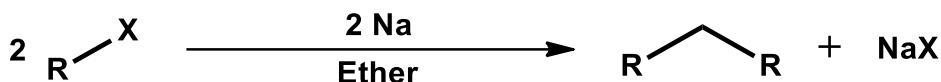
$- H^{\oplus}$

N-substituted amide

Iminol

Although Beckmann rearrangement favors the migration of the substituent on *anti* position with respect to the hydroxy group, in some cases, two possible *N*–substituted amides may be formed due to the isomerization of the initial oxime under the reaction conditions.

➲ ***Example***

Formation of caprolactam from cyclohexanone.

IV. 9. Wurtz Reaction

Named after the Alsatian French chemist *Charles Adolphe Wurtz*, Wurtz reaction is a coupling reaction whereby two alkyl halides react with sodium metal in dry ether solution to form a higher alkane. This reaction is usually carried out with elemental sodium and it involves an organometallic intermediate. In addition to sodium, other metals have been used for Wurtz reaction such as activated copper, indium, iron, silver, zinc, and a mixture of manganese and copper chloride.

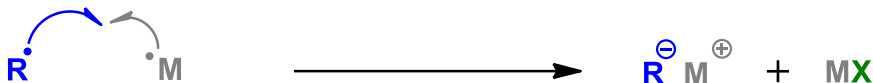
$$2\ R{-}X \xrightarrow[\text{Ether}]{\text{2 Na}} R{-}CH_2{-}R + NaX$$

Mechanism

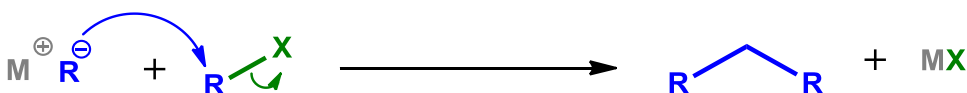
Wurtz reaction proceeds in two steps.

The first step is a halogen-metal exchange through a radical reaction whereby one electron is transferred from the metal to the alkyl halide resulting in a metal halide and an alkyl radical.

$$R{-}X + M \longrightarrow R^{\bullet} + MX$$

At this point, the alkyl free radical would accept an electron from another metal atom to produce an organometallic species, which can be isolated sometimes.

$$R^{\bullet} + {}^{\bullet}M \longrightarrow R^{\ominus}\ M^{\oplus} + MX$$

The second step is a nucleophilic substitution reaction whereby the carbanionic R^- of the organometallic intermediate displaces the halogen atom of another alkyl halide.

$$M^{\oplus}\ R^{\ominus} + R{-}X \longrightarrow R{-}CH_2{-}R + MX$$

Wurtz reaction is limited to symmetrical alkane synthesis. In general, it is not the ideal reaction when it comes to unsymmetrical alkyl halides since it also produces many undesirable side products. In this case, the reaction would yield a mixture of alkanes, which often have insignificant boiling point differences and therefore difficult to separate by fractional distillation. Nevertheless, less side-reactions are observed with intramolecular Wurtz reactions, which makes the reaction efficient in closing small, most notably three-membered, rings. For example, bicyclobutane was prepared via intramolecular Wurtz reaction from 1 -bromo-3-chlorocyclobutane in 95% yield.

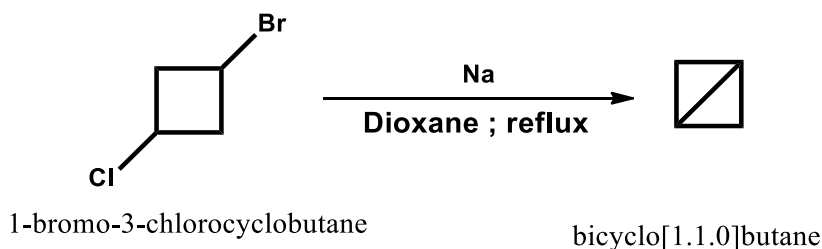
Br

Na

Dioxane ; reflux

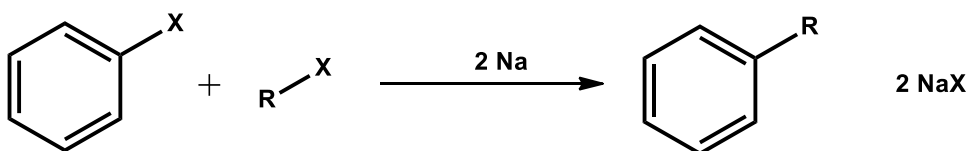
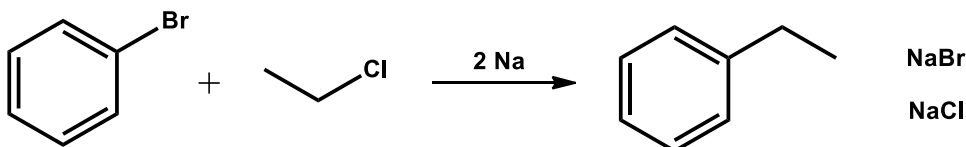
Cl

1-bromo-3-chlorocyclobutane

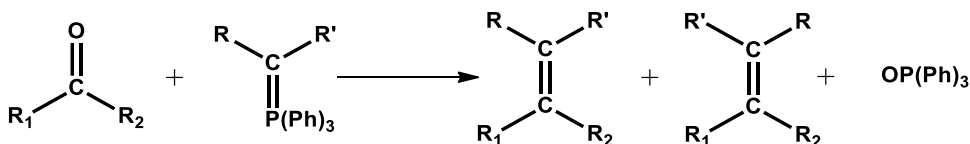
bicyclo[1.1.0]butane

Wurtz-Fittig reaction is a coupling reaction that consists in forming carbon-carbon bonds between an aromatic ring and an aliphatic carbon chain by reacting an alkyl halide with an aryl halide in the presence of sodium in a dry ether solution. This reaction was developed by the German chemist *Wilhelm Rudolph Fittig*, who modified Wurtz reaction by using an aryl halide with an alkyl halide.

X + R—X → (2 Na) → R, 2 NaX

➲ ***Example***

Br + Cl → (2 Na) → NaBr, NaCl

IV. 10. Witting Reaction

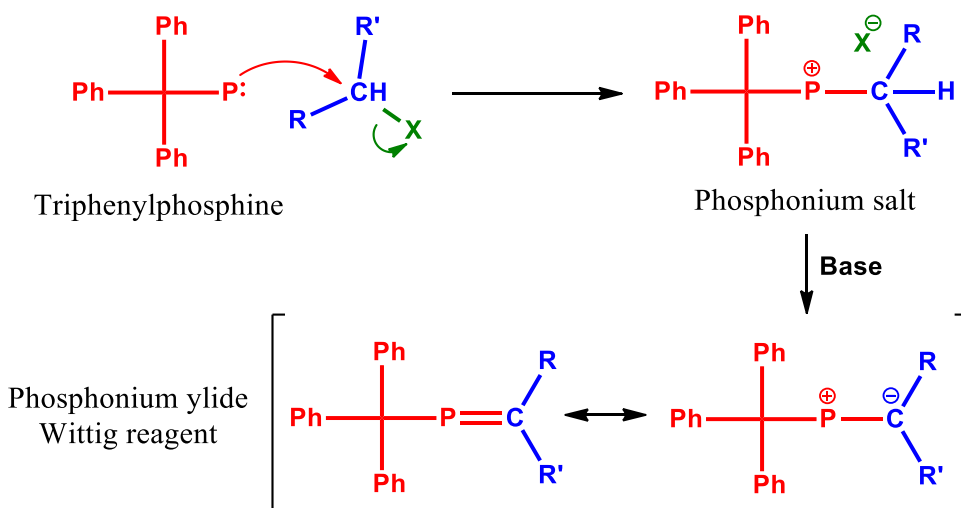
Named after the German chemist *Georg Wittig*, Wittig reaction is a coupling reaction that converts carbonyl function of aldehydes and ketones into a carbon - carbon double bond “alkene” using Wittig reagent “phosphonium ylide”.

$$R_1C(=O)R_2 + RR'C{=}P(Ph)_3 \longrightarrow R_1R_2C{=}CRR' + R_1R_2C{=}CR'R + OP(Ph)_3$$

The most common procedure to produce phosphonium ylide is the reaction of triphenylphosphine with an alkyl halide, which gives a triphenylphosphonium salt followed by a treatment with astrong base such NaH to generate the corresponding Wittig reagent.

Triphenylphosphine

Phosphonium salt

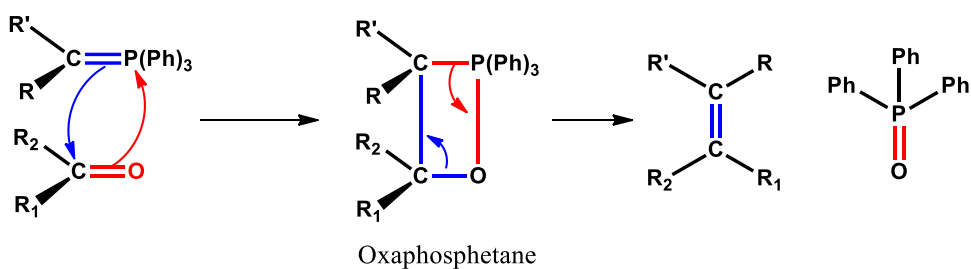
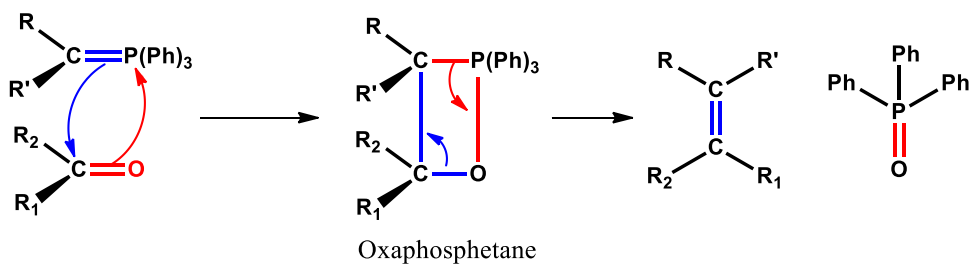
Base

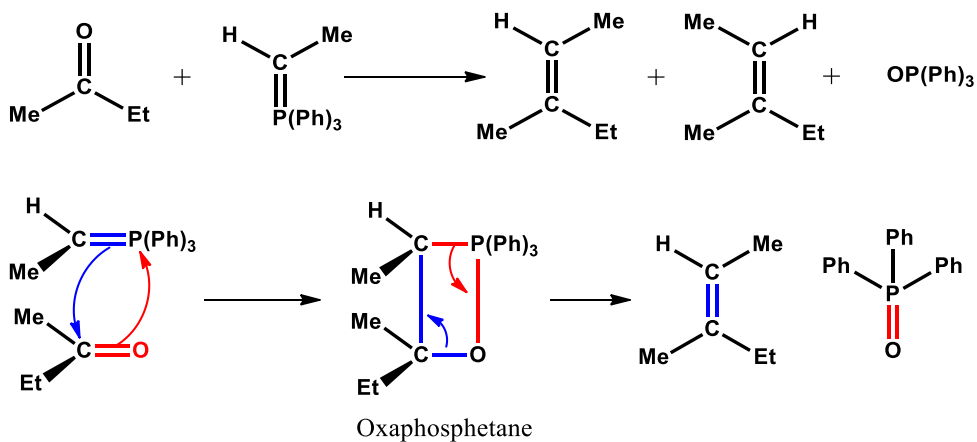
Phosphonium ylide
Wittig reagent

Mechanism

Most recent researches support a concerted addition of phosphonium ylide to the carbonyl group. In particular, phosphonium ylide reacts with the carbonyl compound via a [2+2] cycloaddition to form a four-membered cyclic intermediate called an oxaphosphetane, which then collapses and to form the corresponding alkene with triphenylphosphine oxide $(Ph)_3PO$. Moreover, Wittig reaction tends to give two diastereoisomers E and Z since the phosphonium ylide can add from either

sides of to the carbonyl group. In this case, the ration of E/Z depends upon the structures of both reagents.

Oxaphosphetane

Oxaphosphetane

➲ ***Example***

Oxaphosphetane

Organic Chemistry Reaction Mechanisms Coursebook

This Coursebook will guide you through all fundamental reaction mechanisms that you need to learn in Basic Organic Chemistry with illustrated examples that explain step by step every mechanism taking into account the stereochemistry and regiochemistry of every reaction.

Topics included are:

- Types of solvents.
- Stability of carbocation, free-radical carbon, carbanion, and carbene.
- Nucleophiles, nucleofuges, electrophiles, and electrofuges.
- Free-radical substitution reactions of alkanes, allylic and benzylic compounds.
- Aliphatic and aromatic nucleophilic substitution reactions: SN1, SN1cA, SN1', SN2, SN2', SNAr, SN1 Ar, and SAR2.
- Electrophilic aromatic substitution reactions.
- Elimination reactions: α-elimination, E1, E1cB, E2.
- Addition reactions: nucleophilic, electrophilic, concerted, and free radical.
- Oxidation of functional groups.
- Reduction of functional groups.
- A selection of common named reactions: Grignard reaction, Aldol reaction, Michael addition, Knoevenagel condensation, Claisen condensation, Robinson annulation, Diels-Elder reaction, Beckman rearrangement, Wittig reaction, Wurtz-Fittig reaction.